REACTIVITY OF THE RETINAL PIGMENT EPITHELIUM: AN EXPERIMENTAL AND HISTOPATHOLOGIC STUDY*

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THE PURPOSES OF THIS STUDY were threefold: (1) to appraise the general nature of pigment epithelial reactivity; (2) to analyze and classify ocular lesions in which proliferation of pigment epithelium plays a prominent part; and (3) to determine if patterns produced by pigment epithelial proliferation are sufficiently characteristic to be of clinical value in differential diagnosis.

Even a cursory review of the literature verifies the interest that has been aroused by clinical and histopathologic manifestations of changes in this unique layer of cells. A recent paper by Ferry[1] particularly emphasized the need for further clarification of the role of pigment epithelium in the production of pigmented lesions of the ocular fundus. He examined 529 eyes removed with a clinical diagnosis of malignant melanoma. One hundred of these eyes (19 per cent) proved to contain lesions which were not malignant. Although several different diseases were found, many of these eyes were removed because of ophthalmoscopic evidence of pigmentation. This pigmentation was subsequently shown to have been produced entirely by proliferation of the pigment epithelium. The various aspects of this problem have been discussed in a voluminous literature and reference will be made to this material in appropriate sections throughout the paper.

Before an examination of these problems was started, a pilot study was made to obtain an estimate of the incidence of pigment epithelial hyperplasia in unselected specimens. Of one hundred consecutive eyes removed for clinical cause, and submitted to the Laboratory of

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Ophthalmic Pathology of the Hospital of the University of Pennsylvania, 59 per cent demonstrated hyperplasia of the retinal pigment epithelium. The changes ranged from simple duplication to massive proliferations often accompanied by large collections of connective and osteoid tissues. This demonstrated that pigment epithelial proliferation is a common reaction, and further study was therefore undertaken.

Tissue culture experiments and examination of histopathologic specimens were the principal methods used in pursuit of the major objectives of this study. Both methods contributed to an appraisal of the general nature of pigment epithelial reactivity. Histopathologic findings were used as the basis for an analysis of ocular lesions in which pigment epithelium played a prominent part and for determination of the diagnostic specificity of such lesions. The results of the tissue culture experiments and of the histopathologic studies will be reported separately and will be followed by a résumé of the findings and conclusions.

I. A STUDY OF THE BEHAVIOR OF PIGMENT EPITHELIUM IN TISSUE CULTURE

Sporadic descriptions of the *in vitro* behavior of pigment epithelial cells have appeared in the ophthalmic literature during the past thirty-five years. Kirby,[2] in 1929, reported the successful cultivation of cells from various ocular tissues including those of the retinal pigment epithelium. Fischer[3] emphasized the difficulties of obtaining a pure culture of pigment epithelium. He was able to do so only with a rim of iris epithelial cells which had become adherent to the surface of the lens in chick embryos.

More recent reports include those of Reese and Ehrlich,[4] Barishak,[5] and Pomerat and Littlejohn[6] all of whom were successful in growing pigment epithelium in tissue culture but none of whom achieved a pure culture. All of their preparations included choroidal tissue and showed prominent growth of fibroblasts in addition to growth of epithelium. Reese and Ehrlich were of the opinion that retinal pigment epithelium grew more readily under these conditions than any other cell and that its rapid growth often inhibited proliferation of other cells. Barishak found a difference in growth characteristics when comparing ciliary and iris epithelium with that of the retina. In the latter, mitotic figures were not found except in areas adjacent to the explant. Bisceglie,[7] having observed that pigment cells in his tissue culture experiments were usually accompanied in their growth by mesenchymal cells, concluded that the two types of cells were in some way related.

Experiments were designed to test further the nature of pigment epithelial activity in a controlled environment.

MATERIALS AND METHODS

BIOLOGIC MATERIALS. Several medium preparations were tried for obtaining successful outgrowths of pigment epithelium of the chick embryo retina; the most beneficial one was Medium 199X supplemented with 20% calf serum (Microbiological Associates, Bethesda, Maryland). The medium contained 0.002% phenol red as an indicator. The production of acid metabolites by proliferating cells and, consequently, the need for medium replacement was shown by a change of the red-orange of the freshly prepared medium (pH 7.4) to yellow (pH 7.0). The solution of trypsin (0.025%) was prepared by diluting stock trypsin (2.5%) purchased from Microbiological Associates with Hanks' Balanced Salt Solution. In the preparation of plasma clot cultures, chicken plasma and chicken embryo extract were used. The embryo extract was CEE_{25} obtained by diluting one volume of CEE_{50} (Microbiological Associates) with one volume of medium.

GLASSWARE. The vessels used for the tissue cultures were Earle's T-15 flasks (Kontes Glass Company, Vineland, New Jersey). Flasks and test tubes were closed with special non-toxic stoppers (Kontes Glass Company) #00 for the T-15 flasks, #0 for the test tubes. All Pasteur capillary pipettes, other volumetric pipettes, and test tubes without lip were of pyrex. All glassware was cleaned and sterilized according to standards approved by the Tissue Culture Society.

PREPARATION OF CELL CULTURES. Under aseptic conditions the eyes of seven- to sixteen-day chick embryos were enucleated and the anterior segments excised. After removal of the vitreous and retina from the eye the pigment epithelium and the choroid could be peeled easily from the inner surface of the sclera. Since it was impractical to remove the pigment epithelium from the choroid, the entire thickness of both tissues was used for implantation. The thin layers of tissue were placed in a small sterile petri dish containing a few milliliters of medium 199X with 20% calf serum added. They were then cut into fragments about one millimeter square using two #11 Bard Parker blades. The fragments were washed free of debris by aspirating with fresh portions of complete medium.

PLASMA CLOT PREPARATIONS. In the initial group of experiments plasma clot preparations were made as follows. Using a Pasteur pipette, three or four drops of chicken plasma were carefully spread over the entire floor of a T-15 flask. The flask was left at a slight angle for five minutes, after which excess plasma was removed. Six fragments of tissue were then arranged some distance from each other on the surface of the plasma. They were carefully covered with two or three drops of chick embryo extract (CEE_{25}) which formed a firm clot when it came in contact with the plasma. The flask was stoppered and placed in a standard incubator at 37.5° C. for overnight incubation. Two milliliters of freshly prepared growth medium were then added, and the cultures were re-stoppered and returned to the incubator. Periodic microscopic examinations were made after the first twenty-four hours of incubation to observe the outgrowth. The medium was replaced when change in its color indicated accumulation of acid metabolites. Several replicate cultures were prepared at the same time.

"FEEDER LAYER" PREPARATIONS. In one group of experiments monolayers of chick embryo fibroblasts were prepared on which pigment epithelium could be implanted. The feet, head, wings, and organs from twelve-to-thirteen-day chick embryos were removed. The tissue was washed in Hanks' Balanced Salt Solution, minced with scissors or knife, and placed in an Erlenmeyer flask. One hundred and twenty-five milliliters of 0.025% trypsin in Hanks' Balanced Salt Solution were added and a small Teflon bar, previously sterilized, was introduced into the flask. The trypsin suspension was then stoppered, placed on a magnetic stirrer, and agitated slowly for thirty minutes. The flask was partially immersed in an ice-water bath for five minutes to inactivate the trypsin and the contents were filtered through a layer of sterile coarse gauze. The filtrate was centrifuged at 1000 r.p.m. for five minutes, the supernatant liquid removed with a pipette, and the resultant pellet of cells suspended in fresh growth medium. Cell counts could be made with a standard blood cell counting chamber. Several replicate cultures were prepared by dispensing two-milliliter portions of a cell suspension containing approximately 1×10^6 cells per milliliter into T-15 flasks. These flasks were then incubated in a standard incubator at 37.5° C. When a good monolayer of fibroblasts was observed, usually within the first twenty-four or forty-eight hours after planting, the old medium was removed and fragments of pigment epithelium and choroid were planted on the surface of the monolayers. It was not necessary to provide a clot of chicken plasma and embryo extract since the fragments adhered well to the monolayer of fibroblasts. After allowing incubation for one hour, cultures were fed with complete growth medium and replaced in the incubator. All cultures were examined microscopically after twenty-four hours to determine the presence or absence of outgrowth. All cultures were re-fed by replacing the medium when its color changed.

X-IRRADIATED "FEEDER LAYER" PREPARATIONS. Puck and Marcus[8] reported a beneficial effect on the growth of other types of epithelial cells when cells of the feeder layer had been previously subjected to X-ray. Irradiation effectively prevented the fibroblasts from multiplying although they were still believed to be capable of producing metabolites beneficial to the overlying explants. A small number of replicate cultures was prepared for irradiation experiments as follows. Monolayers of chick embryo fibroblasts were made as in the preceding section. After the monolayer had been incubated until the tissue covered the bottom of the flask the preparations were irradiated by X-ray, each receiving an exposure of 10,200 r. in air. Tissue fragments were then planted on the surface of the monolayer. An equal number of control cultures was prepared at the same time using monolayers which had not been irradiated.

FIXATION, STAINING, AND PHOTOGRAPHY. Photographs of cellular outgrowths were made at suitable intervals through the wall of the tissue culture flask using standard photomicrographic procedures with a camera attached to the laboratory microscope. When stained specimens were desired, small pieces of cover glass were inserted into the tissue culture flasks before preparation of the monolayer of fibroblasts. Pigment epithelial and choroidal fragments were placed over these cover glasses which could be removed when desired, washed, fixed, and stained with standard hematoxylin and eosin using standard histologic staining methods.

RESULTS

Plasma Clot Preparations

Repeated experiments, testing the plasma clot technique, resulted in only slight outgrowth of pigment epithelium. A number of unsuccessful attempts were made to improve results by changing the nutrient medium and the size of the explants. Most of the tissue fragments remained viable over periods as long as three weeks but showed only slight migration of cells away from the edge of the pigment epithelial layer. In a few of the cultures an outgrowth of fibroblasts, apparently from the underlying choroid, was seen after twenty-four hours of incubation. These fibroblasts ultimately formed tongue-like projections of variable size. Cells of the pigment epithelium soon grew out over the surface of these projections. The extent of such growth was limited to areas covered by fibroblasts. Because these areas of extension from the explant were small, the presence or absence of true reproductive growth was questioned. It was apparent, however, that the fibroblastic projections were providing some form of support for the pigment epithelium and experiments using the "feeder layer" principle were prepared to enhance this effect.

"Feeder Layer" Preparations

Optimal outgrowth of pigment epithelial cells from explants of the choroid and pigment epithelium of chick embryos was obtained when a "feeder layer" of chick embryo fibroblasts was used. The peak of activity of this outgrowth was reached after about three days. The fibroblastic monolayer, when properly prepared, consisted of a thin confluent sheet of elongated mononuclear fibroblasts covering the entire floor of the culture flask. Pigment epithelial cells were easily distinguished from fibroblasts by their pigmentation, round or polygonal shape, and large size. They maintained their epithelial characteristics even after prolonged incubation. That reproductive growth was indeed occurring in these colonies was suggested by the large number of epithelial cells filling areas several times the size of the original explants. Furthermore, in more recent pilot experiments using standard chromosomal identification techniques, chromosomes forming typical mitotic patterns have been found in cells at the boundaries of pigment epithelial colonies.

The supportive role of the underlying monolayer was demonstrated repeatedly. Growth was almost always found only in areas of the flask covered completely by the monolayer. When the concentration of cells in the tissue suspension was low, an incomplete monolayer was formed in the flask and growth of epithelium was often limited by the sparse fibroblastic support (Figure 1.) In other experiments the layer of fibroblasts was too heavy and, after a short period of incubation, outgrowth of pigment epithelium was stopped probably by the overgrowth of fibroblasts (Figure 2). The best outgrowth was obtained in those flasks in which the floor was uniformly covered by a true monolayer of fibroblasts (Figure 3).

X-Irradiated "Feeder Layer" Preparations

Attempts to enhance outgrowth of pigment epithelial cells of the chick embryo retina by prior irradiation of the monolayer with X-rays did not seem to be successful. Outgrowth of cells was more rapid in the irradiated group during the first twenty-four hours than in the non-irradiated control group. After three or four days, however, colonies in the two sets of flasks were of about equal size.

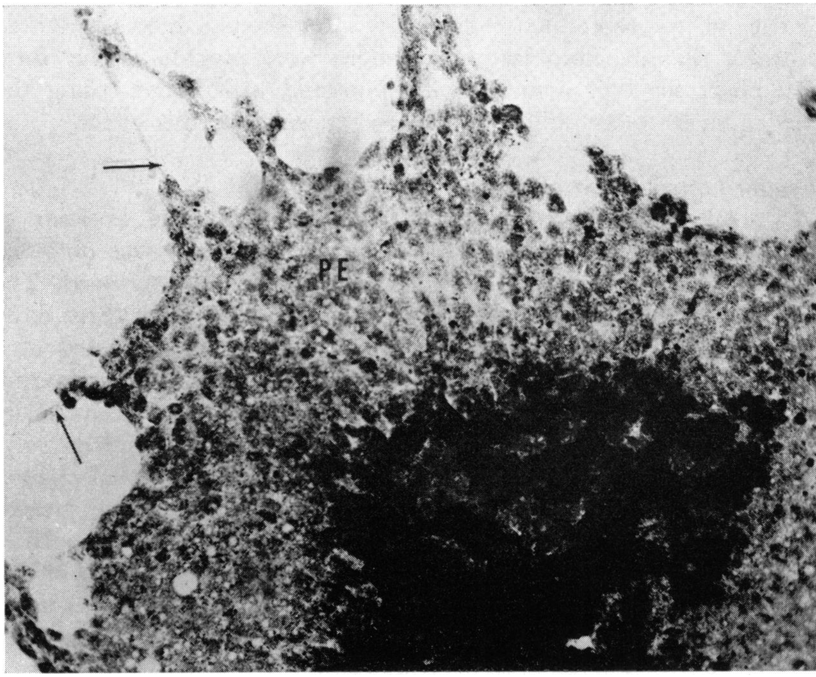

FIGURE 1
Explant of retinal pigment epithelium and choroid of the chick embryo on an incomplete fibroblastic monolayer in tissue culture. Pigment epithelial cells (PE) have extended a short distance from the original heavily pigmented fragment. Further growth is limited because of the absence of fibroblastic support. Some cells extend out along thin strands of the monolayer (arrows). ($\times$ 130)

II. HISTOPATHOLOGIC STUDY OF RETINAL PIGMENT EPITHELIAL REACTIVITY

General reviews have emphasized the frequency and variability of pigment epithelial reactivity in pathologic specimens and have described some of its clinical manifestations.[9–11] A clinical and histopathologic study was made to discover how a knowledge of the pathogenesis of pigmented chorioretinal lesions could be applied to the solution of clinical problems.

Materials and Methods

The files of the Armed Forces Institute of Pathology, Registry of Ophthalmic Pathology, Washington, D.C., and of the Ophthalmic Pathology Laboratory, Hospital of the University of Pennsylvania,

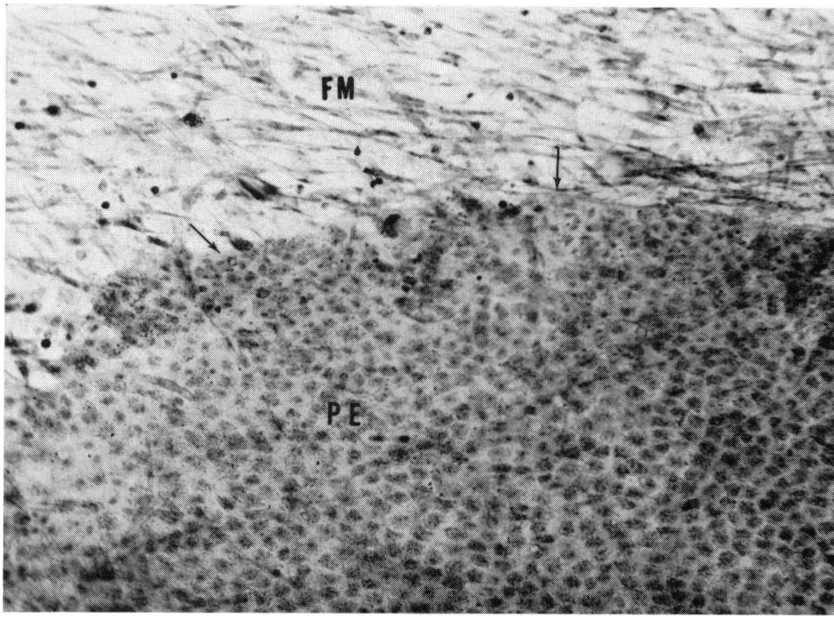

FIGURE 2

Tissue culture preparation similar to that illustrated in Figure 1. Pigment epithelium (PE) is proliferating in a solid sheet but growth has been arrested (arrows) by excessive growth of fibroblastic cells (FM). (× 130)

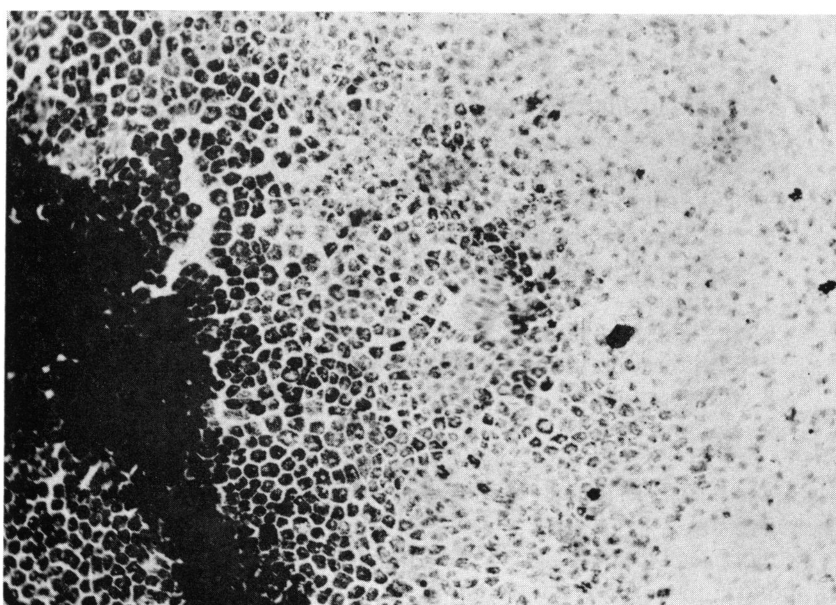

FIGURE 3

Extensive and diffuse growth of pigment epithelial cells in tissue culture over true monolayer of fibroblasts which renders uniform support. The original explant is the darkly pigmented area (lower left). Fibroblasts are completely covered by pigment epithelial cells and are not seen. Epithelial cells lose some of their pigment as they grow but retain their epithelial characteristics. (× 130)

Philadelphia, Pa., were searched for examples of congenital, traumatic, inflammatory, degenerative, and neoplastic diseases accompanied by changes in the pigment epithelium or by other forms of pigmentation. Primary neoplasms of the pigment epithelium were also included in the study. All eyes were evaluated clinically and histopathologically, first to clarify the nature of hyperplasia and secondly to determine the role of the pigment epithelium in the pathogenesis of pigmented lesions of clinical importance.

Results

The results of the clinical and histopathologic study will be described in the following order:

A. The General Pathology of Retinal Pigment Epithelial Hyperplasia
   1. Simple proliferation
   2. Proliferation with formation of cuticular masses
   3. Proliferation with fibrous metaplasia
   4. Proliferation with calcification
   5. Proliferation with ossification
   6. Migration
   7. Proliferation in response to a demand for phagocytes
   8. Pseudoepitheliomatous hyperplasia and true neoplasms

B. The Role of Pigment Epithelium in the Production of Pigmented Chorioretinal Lesions
   1. Primary hyperplasia
   2. Congenital and developmental anomalies
   3. Inflammation and hyperplasia
   4. Degenerative diseases
   5. Trauma
   6. Retinal detachment
   7. Proliferation in response to tumors
   8. Intoxications
   9. Radiant energy

A. THE GENERAL PATHOLOGY OF RETINAL PIGMENT EPITHELIAL HYPERPLASIA

In most eyes hyperplasia of the pigment epithelium seemed to be an integral part of a reparative process apparently stimulated by some type of injury at the chorioretinal junction. It probably contributed materially to the formation of scar tissue having unique histologic characteristics. These scars were usually small and purposeful but when they became excessively large caused extensive damage to surrounding tissues and were sometimes mistaken for melanomas or other tumors.

Klien's[12] classification of pigment epithelial hyperplasia in macular disease has been slightly modified and applied to description of the general patholology of hyperplasia. It is important to recognize, however, that this classification, while useful for descriptive purposes, is not a total reflection of the pathologic changes. Each group represents part of a continuous process and all or part may occur simultaneously.

1. Simple Proliferation

In its simplest form, proliferation of the pigment epithelium is characterized by duplication of cells uncomplicated by metaplasia or production of cuticular material. According to Reese[13] it is the result of a stimulus severe enough to produce hyperplasia but not sufficiently noxious to destroy the pigment epithelium. The sharply circumscribed pigmented lesion in the macula of some myopic eyes, known as Fuchs' spot, has also been cited as an example of simple hyperplasia[12] although Reese[9] has pointed to the similarities between this lesion and the so-called benign nevus of the pigment epithelium. Its cause has not been established.

In this study, simple proliferation was seen most commonly in eyes with retinal detachment, either as a localized cluster of cells (Figure 4) or as a diffuse hyperplasia (Figure 5). Atrophic lesions of the choroid or retina were frequently accompanied by simple proliferation of the pigment epithelium. Small areas of pigmentation were sometimes the most prominent clinical sign, for example, in some of the heredodegenerative diseases characterized by primary atrophy of the retina.

2. Proliferation with Formation of Cuticular Masses

In histologic specimens simple proliferation of the pigment epithelium was often accompanied by a homogeneous, usually eosinophilic material which demonstrated a positive periodic acid-Schiff reaction. Presence of this substance has usually been interpreted as an extension of the physiologic secretory activity of pigment epithelium. In the normal pigment epithelial cell electron photomicrographs have revealed morphologic features usually associated with secretion of mucoproteins and glycoproteins,[14-16] and histochemical evidence of secretory activity has been demonstrated.[17] The basement membrane of the pigment epithelium has been generally regarded as a product of epithelial secretion[18,19] forming the innermost cuticular layer of Bruch's membrane.

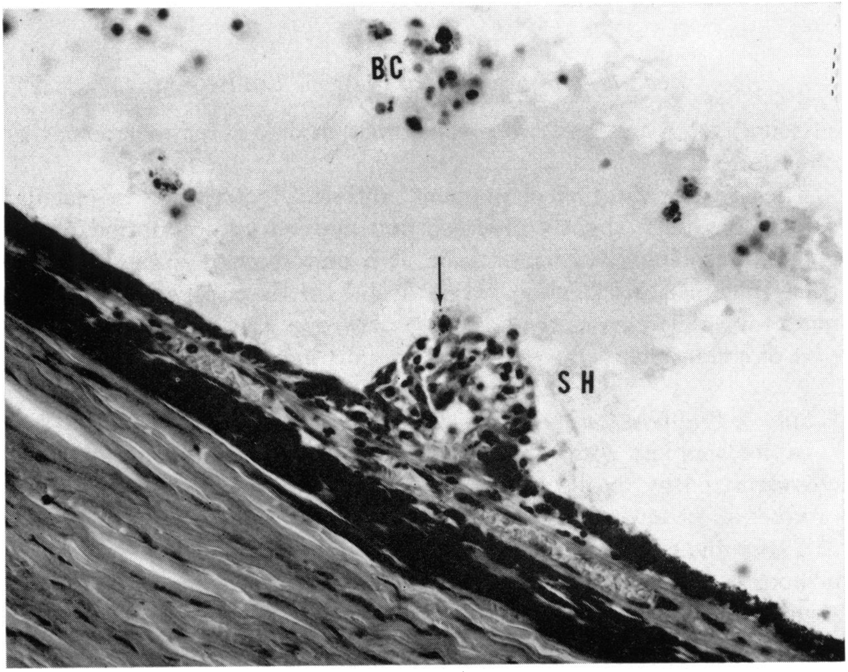

FIGURE 4

Simple hyperplasia (SH) of the retinal pigment epithelium in an eye with retinal detachment. "Bladder cells" (BC) are present in the subretinal fluid. Similar cells with foamy cytoplasm (arrow) appear to be breaking away from the hyperplastic nodule of pigment epithelium. HUP Acc. No. 1495 (× 260)

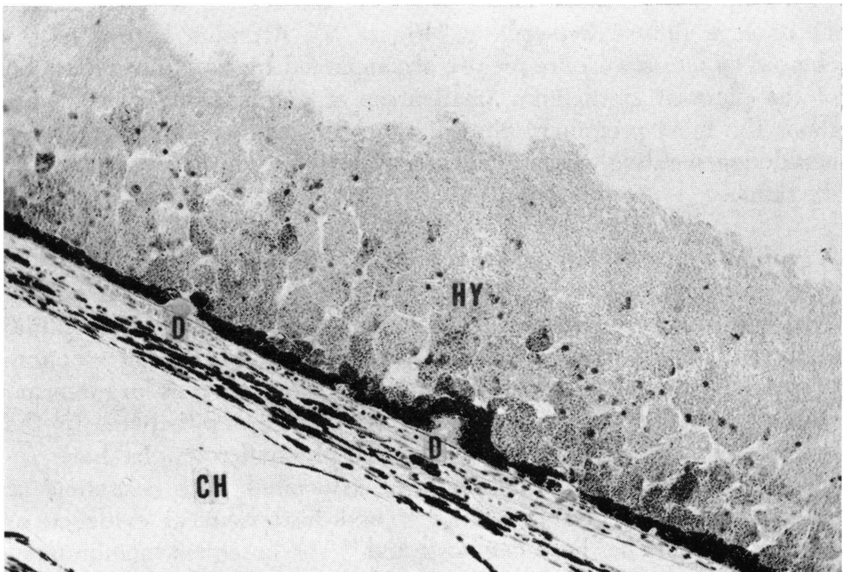

FIGURE 5

Diffuse hyperplasia (HY) in an eye with retinal detachment and hemosiderosis following trauma. The pigment epithelium stained heavily for iron. Several small drusen (D) are found on Bruch's membrane. CH = choroid. AFIP Neg. 64–6261 (× 145)

In pathologic eyes simple drusen served as the best illustration of the cuticular product, now more commonly referred to as basement-membrane–like material (BML) (Figure 5). Although some drusen may be caused by degenerative transformation of pigment epithelial cells, most are considered to be the result of a deposition of BML on Bruch's membrane.[20,21] Drusen were found most often in this study in eyes with retinal detachment but were also found in many eyes with intact retinas, probably as a manifestation of aging.

Hyperplasia with elaboration of thin membranes of BML was seen occasionally in disciform degeneration of the macula (Figure 6) and in small areas of proliferation accompanying retinal detachment (Figure 7). Diffuse thickening of Bruch's membrane occurred in the presence of diseased pigment epithelium and was probably also due to formation of abnormal amounts of BML. Reese[9] has suggested that

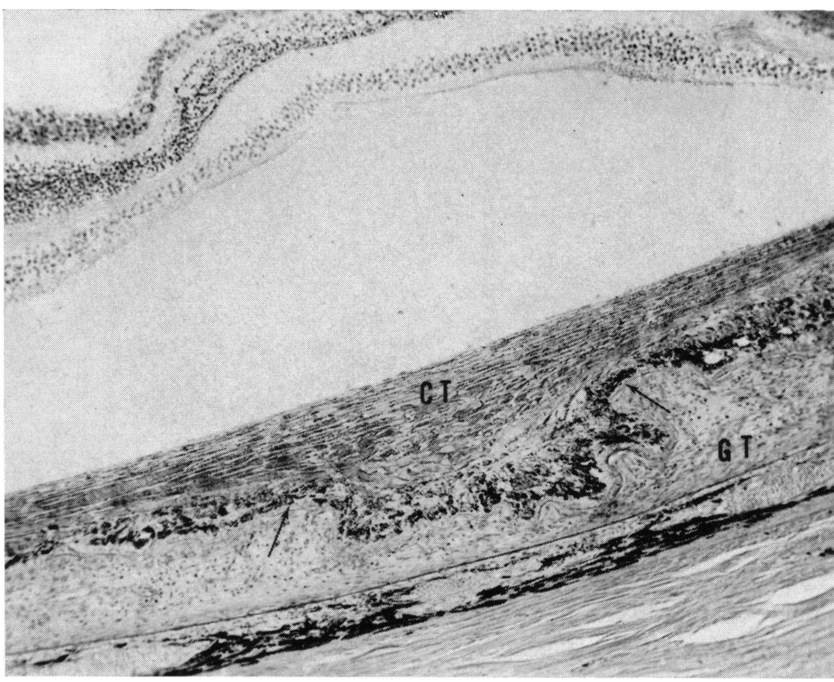

FIGURE 6

Disciform degeneration of the macula. The pigment epithelium has been elevated by a layer of granulation tissue (GT) derived from choroidal vessels. Denser, less cellular connective tissue (CT) has been formed by metaplasia of pigment epithelial cells and lies anterior to them. A new membrane of basement-membrane–like material (arrows) has been elaborated just behind the pigment epithelium. The retina is elevated by a small amount of serous fluid. AFIP Neg. 64–6246 (× 90)

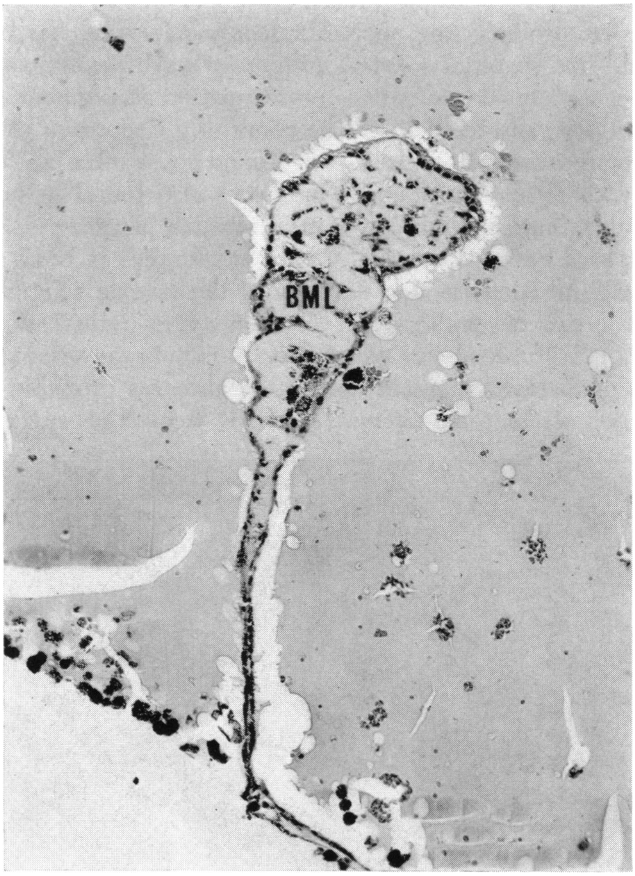

FIGURE 7
Elaboration of basement-membrane–like material (BML) by proliferating pigment epithelium in an eye with retinal detachment. AFIP Neg. 64–6273 ($\times$ 130)

thickening of Bruch's membrane in the macular area might play an important role in the development of senile macular degeneration by interfering with the passage of nutritional substances between the choroid and the retina.

Excessive amounts of BML were present in many hypertrophic scars particularly those in the macular region and always in association with proliferation of pigment epithelium. Although it appeared to be an important component of such scars its exact role, if any, could not be ascertained.

3. Proliferation with Fibrous Metaplasia

The possibilty that fibrous connective tissue and bone might arise directly from pigment epithelium by a process of metaplasia was first suggested, as far as could be determined, by Brailey and Lobo[22] in 1882. Subsequent authors have agreed that pigment epithelium is a major source of fibroblasts in the organization of subretinal scars.[23-27] The fibroblasts produced by metaplasia are similar, in most respects, to those arising from vascular tissues but the histologic appearance of the fibrous tissue which develops from them is slightly different and often appears to contain large amounts of BML.

The classic example of a subretinal scar is found in hemorrhagic disciform degeneration of the macula and will serve to illustrate some of the histologic features of wound healing at the chorioretinal junction. It has been established that, in most instances, this form of macular degeneration is initiated by a hemorrhage beneath the pigment epithelium usually accompanied by a break in the lamina vitrea.[28,29] The space beneath the pigment epithelium occupied by the hemorrhage is organized by vascular granulation tissue originating in the choroid and reaching the subretinal space through the broken membrane (Figure 8). A very dense and entirely avascular layer of connective tissue subsequently develops anterior to the pigment epithelium. This layer is proabably produced largely by metaplasia of pigment epithelial cells and is marked by the presence of homogeneous BML secretions (Figure 6).

During the course of the present histopathologic study scars were seen often in the macula but were also found in other areas. Most of them had features similar to those of disciform degeneration. In some degenerated eyes, with complete retinal detachment, the subretinal space was almost entirely obliterated by a broad membrane of dense, relatively acellular connective tissue with almost no remaining epithelium (Figure 9). Similar scars were found whenever traction on the retina had produced chronic irritation. The largest of these were found at the ora serrata and completely encircled the globe (*Ringschwiele*).

Although pathologic material provided strong evidence favoring an important role for the pigment epithelium in the pathogenesis of subretinal scars, no satisfactory experimental techniques have been developed for the study of this process. A consideration of the general pathology of wound healing in other areas, with particular attention to the part played by epithelial structures, however, provided theoretical clues to the nature of the retinal process.

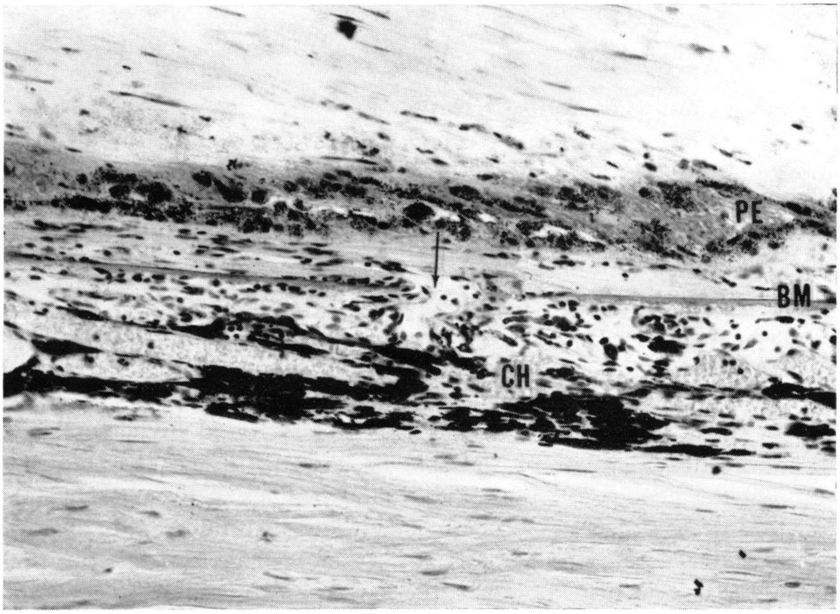

FIGURE 8
Disciform degeneration of the macula. The arrow points to a large vessel extending from the choroid (CH) through a rupture in Bruch's membrane (BM) and into the area of granulation tissue beneath the proliferating pigment epithelium (PE). HUP Acc. No. 859 (× 180)

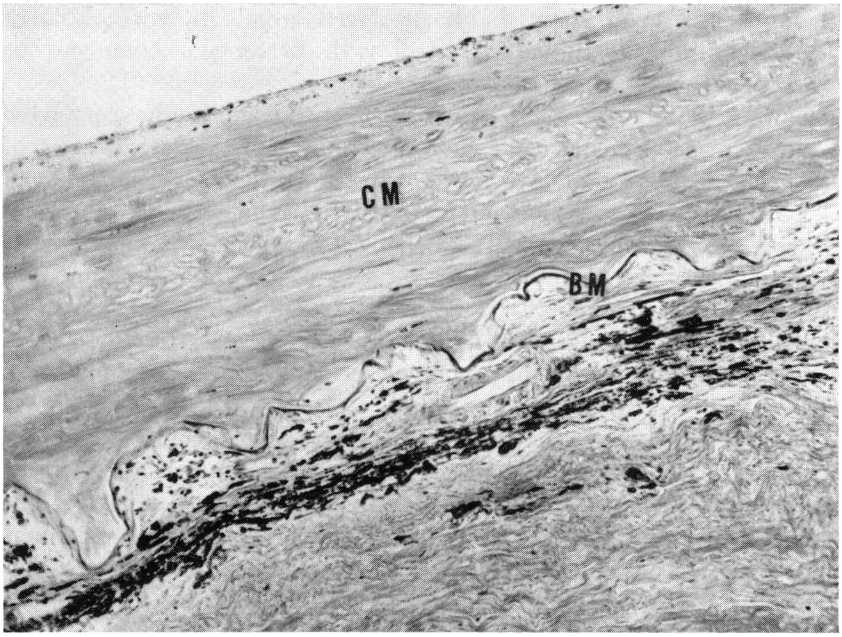

FIGURE 9
Fibrous metaplasia of the retinal pigment epithelium forming a dense collagenous membrane (CM) in front of a degenerated and basophilic Bruch's membrane (BM). HUP Acc. No. 1450 (× 120)

Dunphy and Udupa[30] described wound healing as a complex interaction of various tissue elements at the site of any injury always resulting in some form of scar. Secretion of a collagen precursor by the fibroblast and its interaction with various mucopolysaccharides available in the tissues produced the collagen fiber necessary for the building of mature collagen. Although the fibroblast was the major source of mucoproteins and mucopolysaccharides, these substances might also have been produced by reticuloendothelial cells and probably by some epithelial cells in the area of tissue injury.

A degree of interdependence between epithelial and mesothelial components was suggested by the results of studies on the healing of corneal wounds. Although Herrmann and Lebeau[31] denied the presence of any metabolic interdependence, epithelium was found by Dunnington and Weimar[32,33] to be important for the orderly production of a fibrous scar following experimental incisions of the cornea in rats. The surface epithelium was also credited with an active part in the healing of skin grafts.[34] Epithelial growth in experimental grafts was encouraged by newly formed granulation tissue or fresh blood clot. The epithelium, in turn, appeared to promote fiber formation and to reduce the activity of blood vessels thus tending to reduce formation of exuberant granulation tissue as well. The investigators concluded that hypertrophic scars of the skin might result from a retardation of epithelial growth with consequent overgrowth of underlying connective tissue.

Probably the major function of the pigment epithelial cell in the healing of chorioretinal wounds is to provide many necessary ingredients of scar tissue, such as collagen precursors and acid mucopolysaccharides. In this respect it acts as a fibroblast. It seems reasonable to suggest, however, that some interplay between pigment epithelium and connective tissues from other sources may also play an important role in determining the ultimate configuration of subretinal scars.

4. Proliferation with Calcification

Elongated, sometimes laminated spicules of deeply basophilic calcium salts were found frequently in pathologic specimens, usually in large masses of BML accompanying pigment epithelial proliferation. They were homogeneous or granular and appeared to represent a degenerative change similar to basophilic staining of Bruch's membrane. A more diffuse manifestation of this change was found frequently in large drusen of degenerated eyes.

5. Proliferation with Ossification

True bone, occurring as a late degenerative change in the eye, was characterized by many of the histologic features of membranous bone. Scattered areas of fat and, in the eyes of younger individuals, hematopoiesis were found within its marrow spaces.

The origin of intraocular bone formation has been the subject of lengthy discussions in the older literature. Knapp[35] and Snowball,[36] for example, noted that it was always found behind the membrane of Bruch and believed that it arose from connective tissue surrounding the vessels of the choriocapillaris. Others[22,24] held that it arose anterior to Bruch's membrane in association with the pigment epithelium. Eyes in various stages of degeneration were included in the present study. Whenever new bone was found in the presence of an intact and recognizable lamina vitrea, it was confined to the area anterior to this structure and was usually associated with some degree of fibrous metaplasia of the pigment epithelium. Except in the area immediately adjacent to the optic nerve, ossification was never found beneath Bruch's membrane unless this barrier had been destroyed, permitting invasion of the choroid by proliferating pigment epithelial cells.

In many eyes the pigment epithelium showed its most active hyperplasia in areas immediately surrounding spicules of new bone (Figure 10). Whether this was the result of stimulation by new bone or a factor in its development could not be determined. The pigment epithelium might play a dual role, however, in the production of true bone.[37] First, it has been shown that it may form an eosinophilic matrix which, like osteoid, eventually becomes calcified. Later, it might very well exert an "organizer" influence on the mesenchymal cells to produce the characteristic structure of bone.

6. Migration of Pigment Epithelium

A feature of many proliferative lesions of the pigment epithelium was the migration of cells to other parts of the eye. Secondary lesions produced by continued proliferation and metaplasia of these migrating cells could be of diagnostic value and might even influence adversely the therapy of retinal disease. Pigment epithelial cells reached distant areas in one of two ways: (*a*) by the passage of free, low cohesive or desquamated pigment epithelial cells or groups of cells through intraocular fluids and tissues; (*b*) by proliferation to form continuous sheets along the surface of existing or newly formed smooth membranes.

Many examples of free migration were seen during the course of

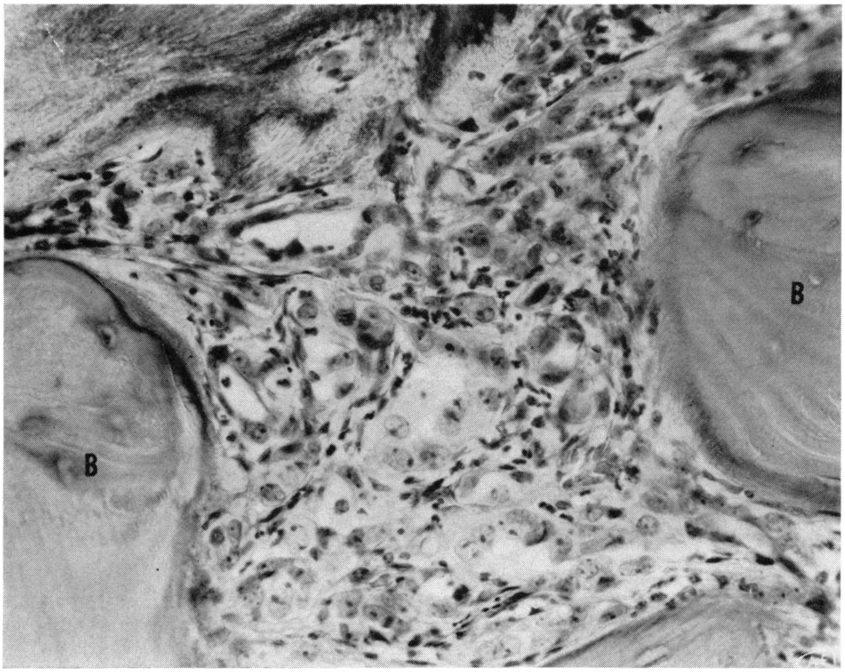

FIGURE 10
Proliferation of pigment epithelium with ossification. The bone spicules (B) are surrounded by large cells with pale staining nuclei which were believed to have been derived from pigment epithelium. AFIP Neg. 64–6238 ($\times$ 300)

the study. In eyes with extensive retinal detachments, cells apparently of pigment epithelial origin were found free within the subretinal fluid presumably having broken away from small foci of simple hyperplasia (Figure 4). Similar cells were found adherent to the posterior surface of the retina where they continued to proliferate, spreading laterally in all directions. In some eyes isolated groups of pigmented cells within the retina resulted from migration and subsequent proliferation of pigment epithelium; in others they were evidently composed of macrophages filled with pigment.

Migration of retinal pigment epithelium along smooth surfaces formed pigmented membranes of variable configuration. This migratory property was one of some importance in the healing process. Proliferation of pigment epithelium through retinal tears in eyes with retinal detachment was described by Kurz and Zimmerman[10] and other examples were found during this study. Thin membranes were formed

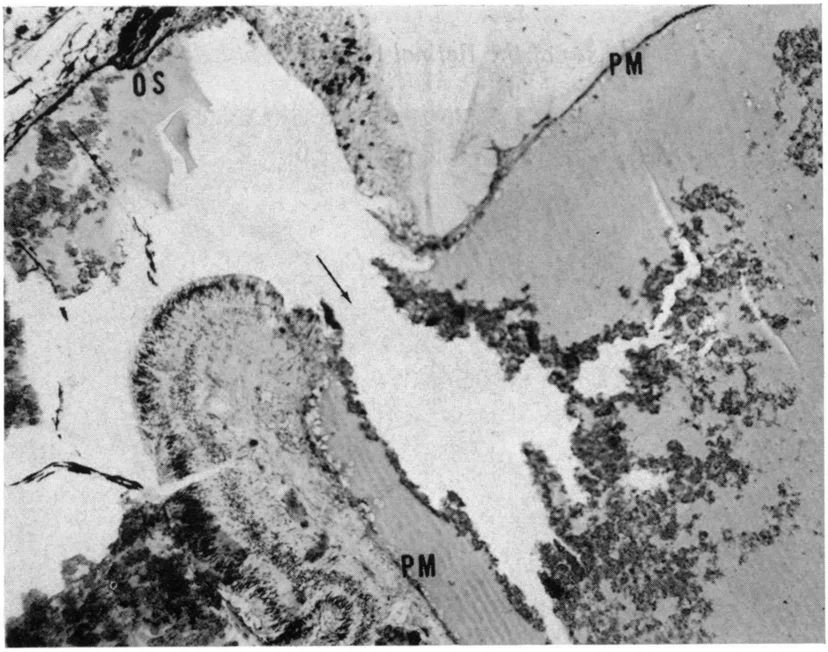

FIGURE 11

Migration of pigment epithelium through a retinal hole (arrow) to form pigmented membranes (PM) on the surface of the retina and on a vitreous surface. The retinal hole is close to the ora serrata (OS). HUP Acc. No. 2136 (× 42)

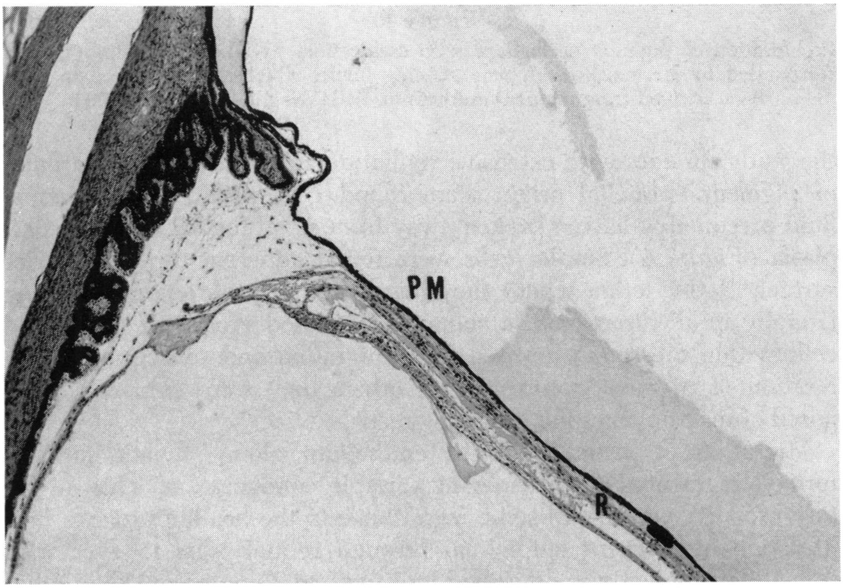

FIGURE 12

A dense pigmented membrane (PM) produced by migration of pigment epithelium from the ciliary body over the surface of a completely detached retina (R). AFIP Neg. 64–6257 (× 50) extending for some distance over the surface of the retina and within the vitreous cavity (Figure 11). The pigment epithelium of the ciliary body formed even heavier membranes which sometimes covered the entire retina (Figure 12).

Strands of vitreous also encouraged the proliferation of retinal pigment epithelium and, in a number of eyes, particularly after penetrating injuries, extensive hyperplasia was seen within the vitreous cavity (Figure 13). Because of the fibrillar nature of the vitreous, the pigment

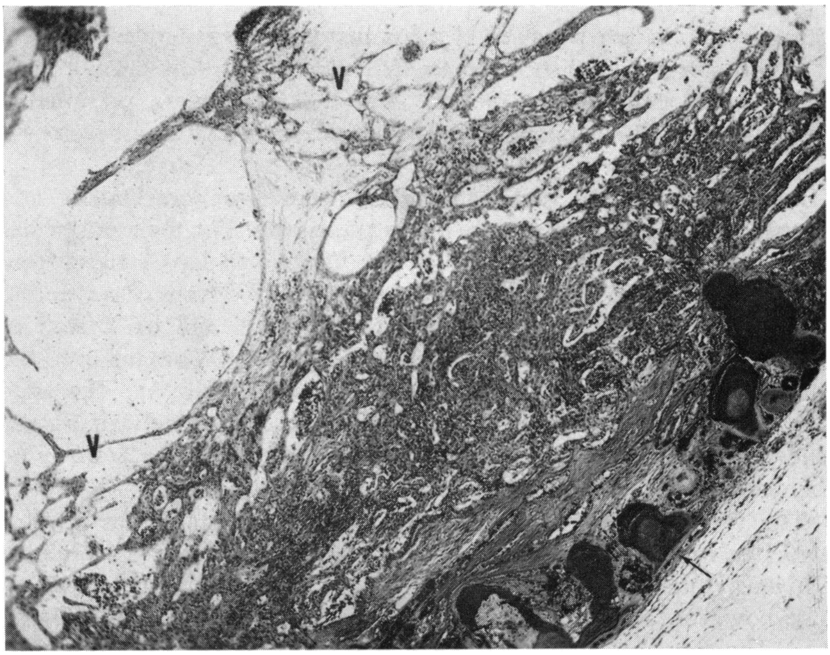

FIGURE 13

Migration of proliferating pigment epithelium along vitreous strands (V) in an eye degenerating as a result of injury. The retina has been destroyed in this area allowing the pigment epithelium to reach the vitreous. The growth closely resembles that seen in tissue culture. On the surface of Bruch's membrane (arrow) are large calcified drusen. AFIP Neg. 65–12273 (× 40)

epithelial cells usually did not form single membranes but grew in branching sheets resembling the growth of cells in tissue culture. The cells were often almost entirely devoid of pigment.

Other smooth surfaces were those provided by newly formed connective tissue sometimes itself derived from metaplasia of pigment epithelium. In cyclitic membranes, for example, and in membranes behind the retina, growth of the pigment epithelium was often prominent and was found both on the surfaces of the membranes and within their substance. Although connective tissue membranes appeared to have provided bridges for the growth of epithelium, the epithelium, in turn, might have been an essential ingredient for the formation of still more connective tissue.

7. Proliferation in Response to a Demand for Phagocytes

An important part of any healing process is the removal from the tissues of particulate products of inflammatory or degenerative disease. It is normally accomplished chiefly by leukocytes and by cells derived from reticuloendothelial sources. Any cell, however, presumably including the retinal pigment epithelial cell, may act as a phagocyte if necessary.[38]

Large foamy cells, found in certain exudative detachments and known as bladder cells, are obviously phagocytic but their origin has been disputed. They were thought by Coats[39] to have arisen from leukocytes, by DeSchweinitz and Shumway[40] to be from degeneration of rods and cones, by Marshall and Michaelson[41] and by Duke[42] to come from histiocytes of reticuloendothelial origin. Others believed the foamy cells were derived from pigment epithelial cells.[43–45] The issue has not been resolved and is probably of little practical importance since macrophages may reasonably be expected to arise from more than one source.

The present study of pathologic eyes uncovered no unequivocal evidence of phagocytosis by cells of the retinal pigment epithelium. Obviously phagocytic multinucleated giant cells were found occasionally, however, and were possibly of pigment epithelial origin (Figure 14). The function of the large multinucleated cells was not clearly indicated in many instances. Sometimes, however, cholesterol had clearly incited the foreign body giant cell response especially in eyes with hemorrhagic retinal detachments (Figure 15).

8. Pseudoepitheliomatous Hyperplasia and True Neoplasms of the Pigment Epithelium

Hyperplasia of the pigment epithelium sometimes took the form of an expanding mass easily mistaken for neoplasm by the examining ophthalmologist. A number of eyes containing such tumors were enucleated and it soon became evident that even histopathologic diagnosis was difficult. Many of the previously reported neoplasms

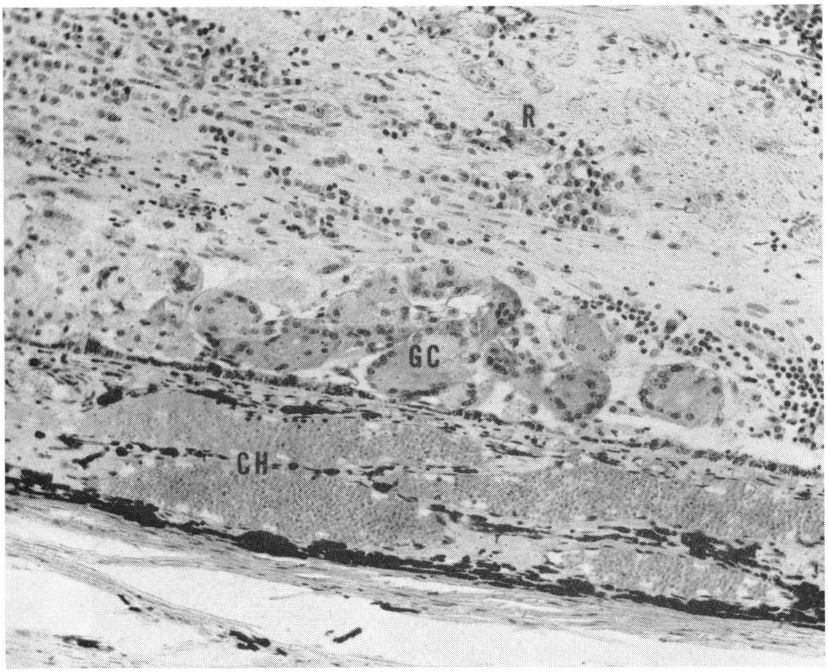

FIGURE 14
Multinucleated giant cells (GC) in a large hypertrophic scar of the macula. The eye was enucleated because of suspected retinoblastoma in an eight-year-old boy. The cells appear to have arisen from pigment epihtelium. Retina (R) is partially replaced by glial tissue and proliferating pigment epithelium. CH = choroid. AFIP Neg. 64–6254 ($\times$ 145)

of the retinal pigment epithelium were, in fact, examples of pseudoepitheliomatous hyperplasia but a few were apparently true neoplasms probably originating in inflammatory foci. Still fewer were evidently true neoplasms occurring in the absence of any signs of inflammation and were, therefore, believed to be spontaneous. The literature on this subject has been thoroughly reviewed.[13,46,47] During the course of this study the histologic characteristics of a number of tumors and pseudotumors of the pigment epithelium were analyzed, however, and have been illustrated in the accompanying photomicrographs.

An example of pseudoepitheliomatous hyperplasia reported by Stow[48] (Figures 16 and 17) was found in the eye of a forty-nine-year-old man with gradually diminishing vision. A large tumor over the optic nerve had been diagnosed clinically as angiomatosis of the

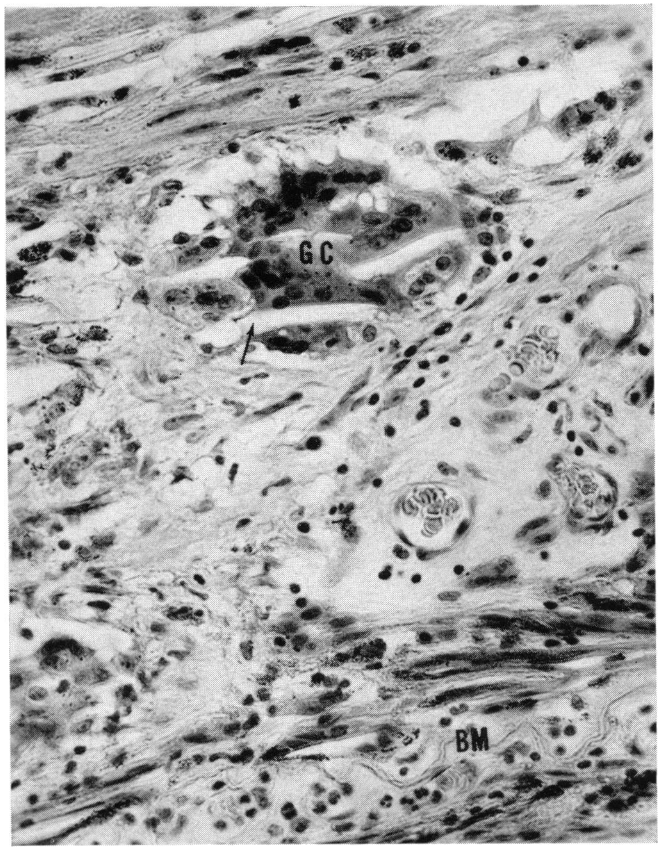

FIGURE 15
Hyperplasia of retinal pigment epithelium after subretinal hemorrhage. Cholesterol crystal clefts are surrounded by foreign body giant cells (GC) possibly arising from pigment epithelium. BM = Bruch's membrane. AFIP Neg. 65–12276 ($\times$ 300)

retina. The well-differentiated cells, growing in regular columns and separated by BML elements, clearly established it as a benign hyperplasia. Its cause was not discovered.

An adenocarcinoma of the pigment epithelium reported by Fair[47] (Figures 18 and 19) was obtained from a twenty-six-year-old woman who had been followed for two years with a gradually expanding lesion near the optic disc. The lesion had originally been thought to be inflammatory because of an exudative reaction in the retina and vitreous. Histologic sections, however, showed only minimal evidence

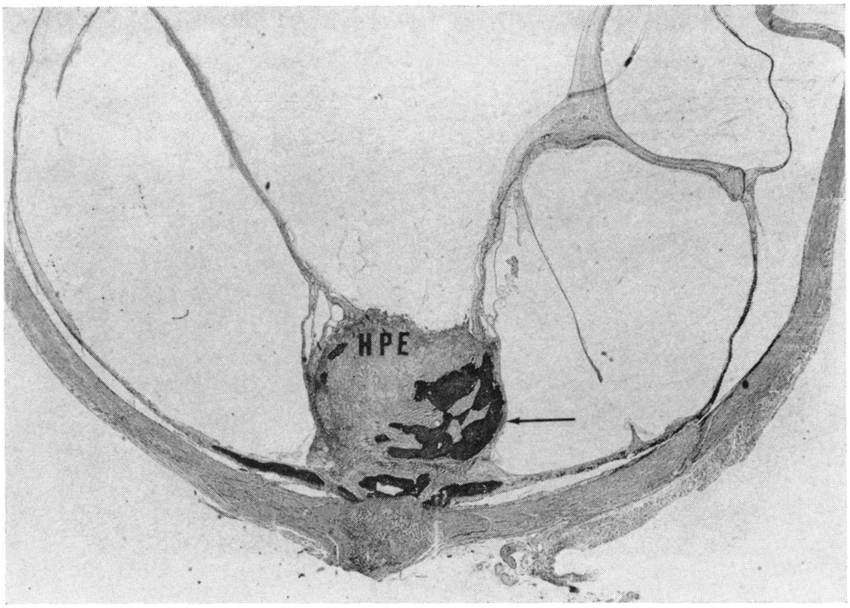

FIGURE 16
Pseudoepitheliomatous hyperplasia of pigment epithelium (HPE) over the optic disc. Osseous metaplasia (arrow) was present within the mass and adjacent to it. The clinical diagnosis was angiomatosis. (Case reported by Stow) AFIP Neg. 187762–7

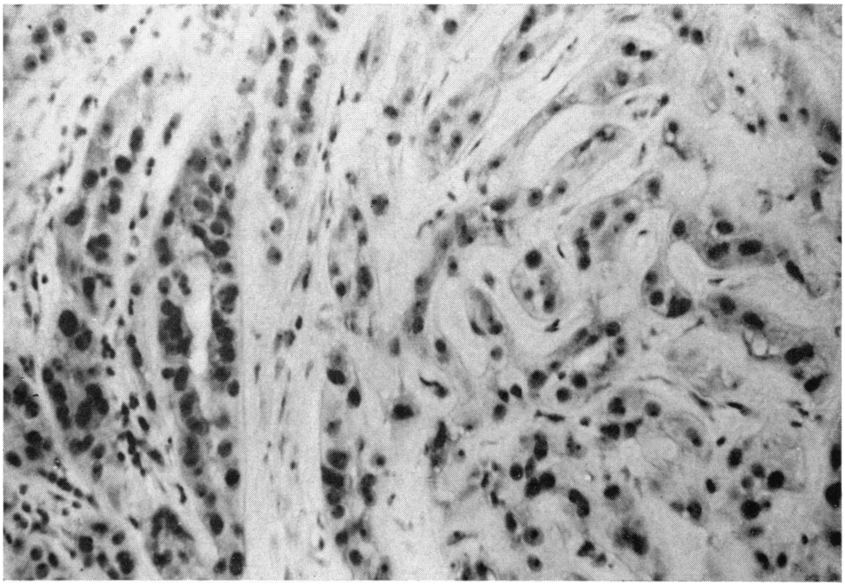

FIGURE 17
Higher magnification of the lesion shown in Figure 16. Well-differentiated pigment epithelial cells are proliferating in orderly columns separated by BML secretions and fibrous tissue. AFIP Neg. 187762–6

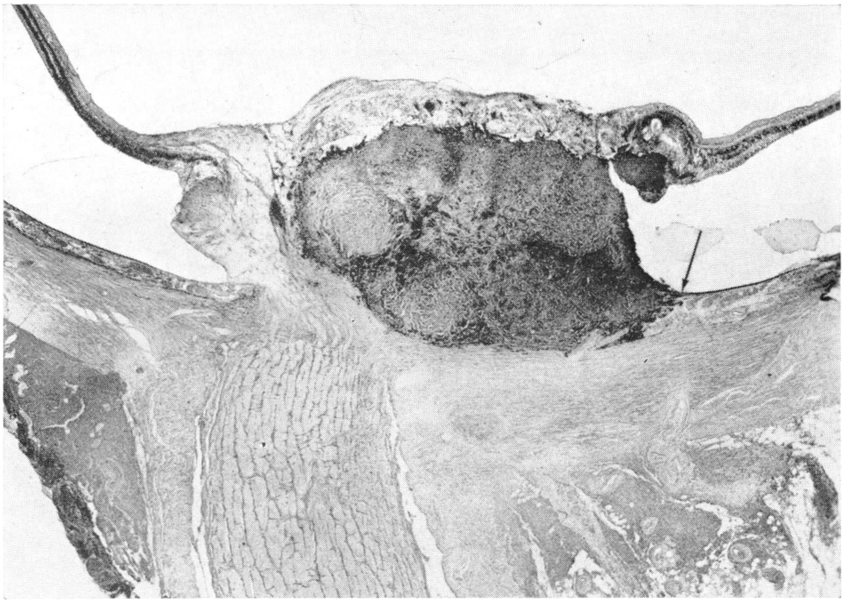

FIGURE 18
Primary adenocarcinoma of the pigment epithelium. There was clinical evidence to suggest that the tumor might have arisen from an inflammatory focus. Invasion of the choroid (arrow) is one sign suggesting that this is a true neoplasm. (Case reported by Fair.) AFIP Neg. 60–6785 (× 12)

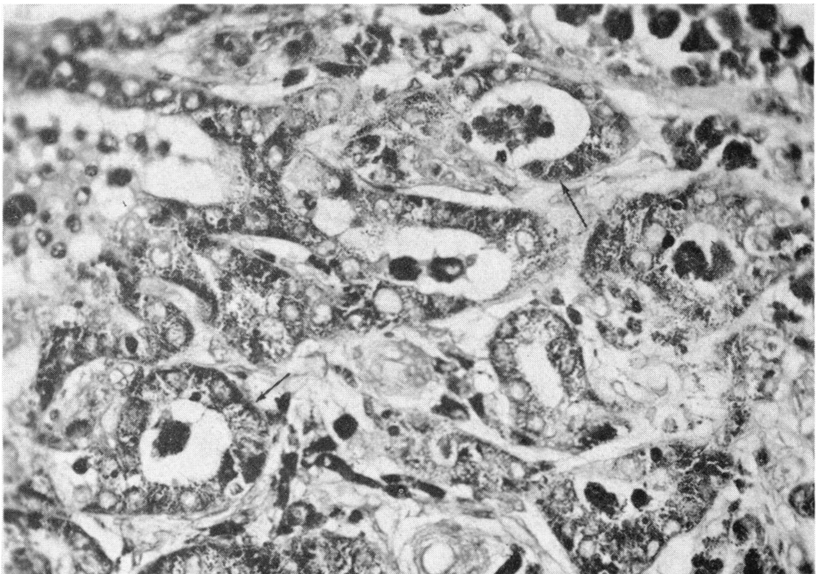

FIGURE 19
Poorly differentiated cells of the tumor illustrated in Figure 18. The gland-like structures formed by these cells were found in most areas of the tumor. AFIP Neg. 60–6787 (× 305)

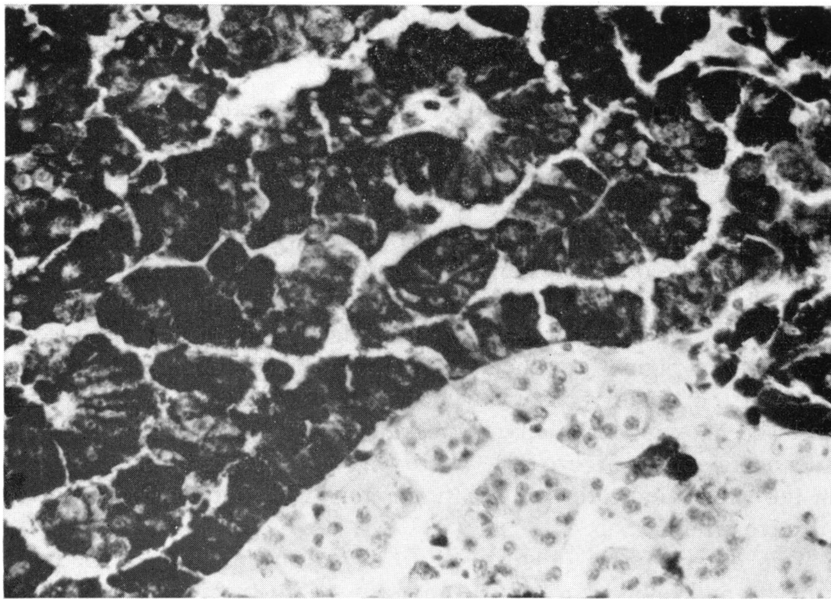

FIGURE 20

Primary adenocarcinoma of the pigment epithelium. The tumor cells, some without pigment, show better differentiation than those in Figure 19 but their arrangement is that of an adenocarcinoma. (Case reported by Kurz and Zimmerman.) AFIP Acc. No. 848819 (× 265)

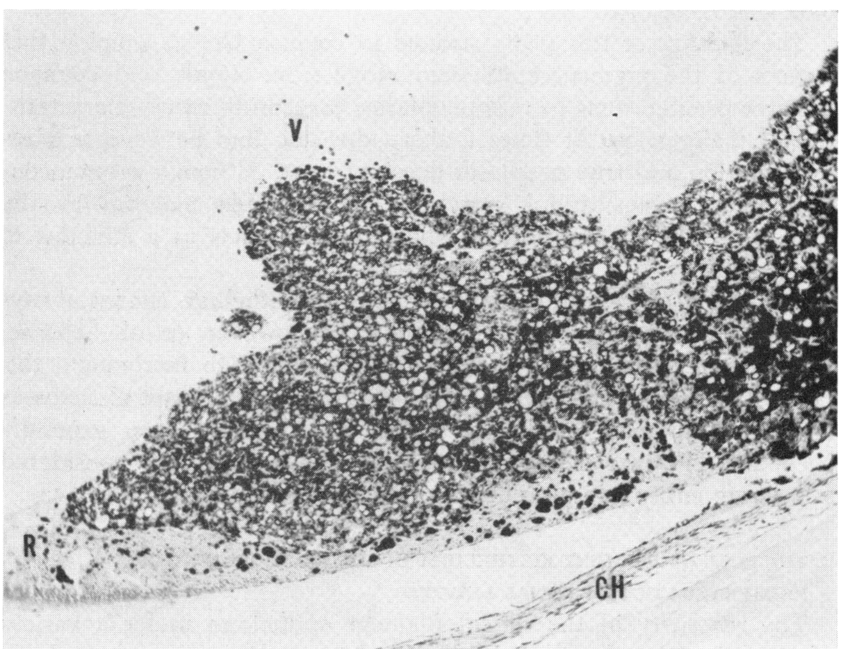

FIGURE 21

Primary adenocarcinoma of the pigment epithelium. This tumor has invaded and destroyed the retina (R) and has extended into the vitreous (V). CH = choroid. AFIP Neg. 64–7092 (× 50) of inflammation and the origin of the tumor remained in doubt. The pattern of cell growth suggested a malignant lesion since the cells were pleomorphic and atypical and the overlying retina had been invaded.

An apparently spontaneous tumor in a fifty-six-year-old caucasian woman was reported by Kurz and Zimmerman.[10] It was characterized clinically by a "large, dark, solid, non-illuminating tumor arising anterior to the equator nasally and slightly inferiorly." The cells, obviously of pigment epithelial origin, were better differentiated than those in the tumor reported by Fair, but their arrangement, in cords and sheets, with invasion of the retina and choroid suggested an adenocarcinoma (Figure 20). There was no evidence of other disease in the eye to indicate that the tumor might have been the result of reactive proliferation.

Two other tumors (Figures 21 to 23) also appeared to be spontaneous and showed cytologic and growth features suggesting that they were malignant neoplasms. In one of them (Figure 23) some of the cells were reminiscent of normal hexagonal pigment epithelial cells but, in other areas, there was marked pleomorphism and many mitotic figures were seen. No clinical evidence was known which indicated metastasis.

The findings of this study seemed to confirm Greer's opinion that tumors of the pigment epithelium range from simple and common reactive proliferations to rare neoplasms presenting many characteristics of malignancy. At times a sharp dividing line between reactive proliferation and true neoplasm does not exist. Although spontaneous tumors do arise, careful search of all available material usually reveals an inflammatory lesion which probably acts as a stimulus to the growth.

The origin of these tumors from pigment epithelium cannot always be established with certainty. Fortunately, however, cellular characteristics are often retained with sufficient clarity to incriminate this layer. Although a few authors have held that all malignant melanomas arise from pigment epithelium[49] this view has not been generally accepted. The rare neoplasm described above should be considered a separate entity and classified as an adenocarcinoma.

B. THE ROLE OF PIGMENT EPITHELIUM IN THE DEVELOPMENT OF PIGMENTED CHORIORETINAL LESIONS

The reactivity of the retinal pigment epithelium under a variety of conditions has been established and its manifestations have been

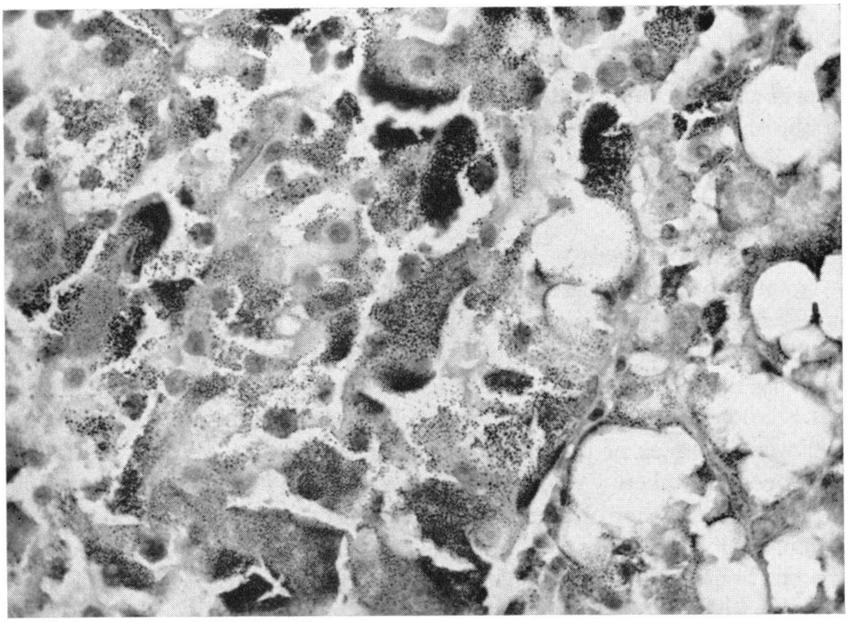

FIGURE 22

Bleached section of tumor shown in Figure 21. The cells are pleomorphic and atypical and have no specific arrangement. AFIP Neg. 64–7093 (× 395)

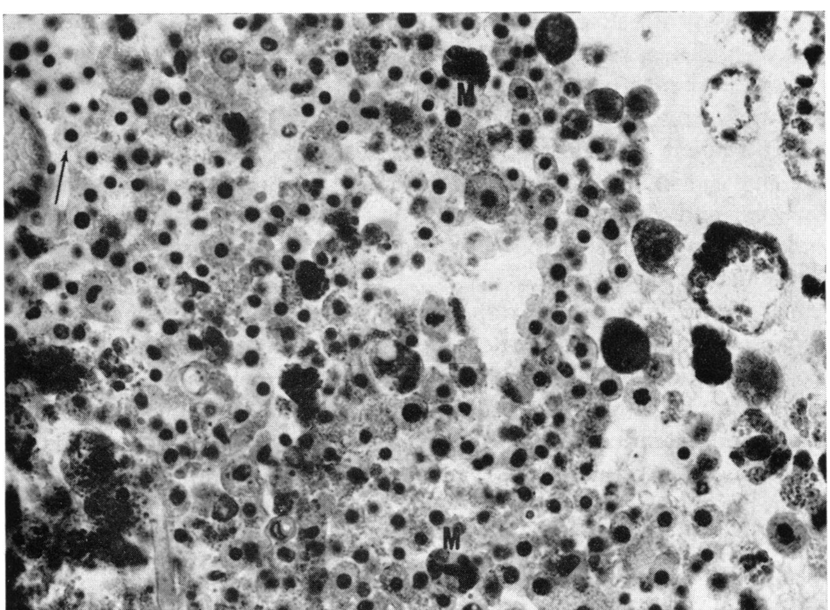

FIGURE 23

Adenocarcinoma of pigment epithelium. Cell outlines are distinct and, in some, are hexagonal (arrow). The appearance is reminiscent of flat preparations of normal pigment epithelium. There is marked pleomorphism, however, and many abnormal mitotic figures (M) are found. AFIP Neg. 64–7090 (× 395) classified. It is important to determine what part these changes have in the development of certain lesions of the choroid and retina and to ascertain what features might be useful in the diagnosis of such lesions.

1. Primary Hyperplasia

Isolated brown or black lesions of the ocular fundus resulting from proliferation of the pigment epithelium and lacking evidence of a specific inflammatory stimulus have been reported as examples of primary hyperplasia.[9,50,51]. These lesions were usually adjacent to the optic nerve and slightly elevated. The eyes had been enucleated because the areas of pigmentation were believed to be enlarging and had been mistakenly diagnosed as neoplasms. During the course of this study a number of eyes were encountered which contained similar lesions. All had shown clinical evidence of expanding pigmented lesions believed to be neoplastic. Histologically, these were of two types, both occurring adjacent to the optic nerve.

One of these types was illustrated by a lesion reported by Spiers and Jensen[52] (Figure 24). The eye was from a ten-year-old girl with vision reduced to 6/60 in the left eye apparently as a result of an elevated gray tumor partially hiding the temporal side of the disc. A mass of pseudoepitheliomatous hyperplasia of the pigment epithelium was found beneath the retina adjacent to the nerve. Inflammatory cells were present in the choroid beneath the lesion but no specific etiologic agent was demonstrated in serial sections. Lesions of this type have sometimes resulted from infestations by nematodes,[53] however, and they should always be serially sectioned.[54] Although similar lesions might be found in other areas this type seemed to have a predilection for the disc area.[13]

In a second group of juxtapapillary lesions without specific cause, the pigment epithelium of the retina had proliferated in single layers into the optic nerve and into the retina. Membranes of pigment epithelium with BML material and glial connective tissue surrounded vessels and extended onto the anterior surface of the retina. Contraction of these membranes often produced retinal folding. Both of the eyes reported by Theobald, Floyd, and Kirk[50] were of this type. A third eye (Figure 25) was from a thirty-two-year-old man whose vision had gradually diminished over a period of nine years. The retina was elevated and thrown into folds by what appeared to be a dark mass next to the disc. Vision in the eye was reduced to 20/60 and a central scotoma was found. The eye was enucleated because a tumor of the

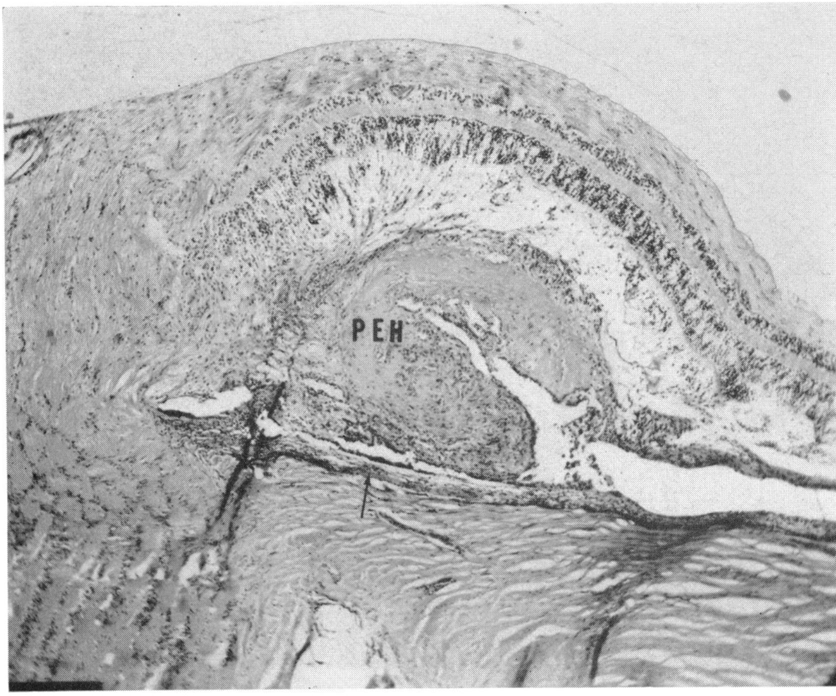

FIGURE 24
Small nodule of pigment epithelial hyperplasia (PEH) adjacent to the optic nerve in a ten-year-old girl. The eye was enucleated with a mistaken diagnosis of glioma of the optic nerve. Study of serial sections failed to provide an etiologic diagnosis. A few inflammatory cells were found in the choroid (arrow). AFIP Neg. 65–12277 (× 40)

optic nerve was suspected. In still another eye, the lesion had been followed for twenty years during which time it had gradually become larger. In all eyes with lesions of this type, expansion of the lesion was believed to be the result of continued proliferation of pigment epithelium and contraction of the membrane on the retinal surface. In none of them could the etiology be determined.

A peripheral lesion, cited by Reese[9] as an example of primary hyperplasia, was reported by Duke and Maumenee[55] who found a localized area of retinal pigmentation in an eye with a retinal detachment. Its histologic pattern, however, was characterized by hypertrophy and hyperpigmentation of the pigment epithelium and was similar to that of a benign congenital nevus of the pigment epithelium.

FIGURE 25
"Primary" hyperplasia of the retinal pigment epithelium in an eye enucleated because of suspected neoplasm. Pigment epithelium of the retina has proliferated in single colums (arrows) through the retina (R) and onto its anterior surface. These pigmented membrances are accompanied by connective tissue, contraction of which has thrown the internal limiting membrane (LM) and the retina into folds. There is inflammation in the choroid (CH) and Bruch's membrane is thickened. AFIP Acc. No. 1157526 (× 75)

2. *Congenital and Developmental Anomalies*

Abnormal pigmentaiton accompanying congenital and developmental anomalies is encountered commonly by the ophthalmologist and its interpretation is of some importance in diagnosis. Such pigmentation may be the result of hyperplasia of the pigment epithelium responding to some intrauterine stimulus but, more often, it indicates an abnormal differentiation of the layers of the primitive optic vesicle.

The pigment epithelium of the retina, derived from the outer layer of the optic cup, normally exerts an important organizing influence on the developing inner sensory layer of the retina as well as on the underlying choroid.[56] Dysplasias of the pigment epithelium, therefore, not only cause obvious disturbances of pigmentation but also result in defects of the tissues on either side of it. Typical colobomas of the retina and choroid, for example, are caused by a localized failure of differentiation of the pigment epithelium. Pigmentation is, therefore, not a prominent feature of the anomaly but the choroid and the retina may be entirely absent.

Atypical colobomas on the other hand, occurring either at the site of the fetal cleft or in other areas of the fundus, are the result of a different mechanism and pigmentation may be prominent. Klien[57] suggested that these atypical forms might be due to folding or to faults in differentiation of the pigment epithelium but not to its absence. Rones[58] attributed them to loss of growth energy at various points along the rim of the optic cup. In either case, pigmentation is a distinctive feature of the lesion and its presence does not necessarily imply an intrauterine inflammation.

A few colobomas of the optic nerve were examined during the present study. They were often characterized by clinical and histologic evidence of pigmentation around the rim and, occasionally, the entire coloboma was lined by pigmented cells (Figure 26). In some eyes

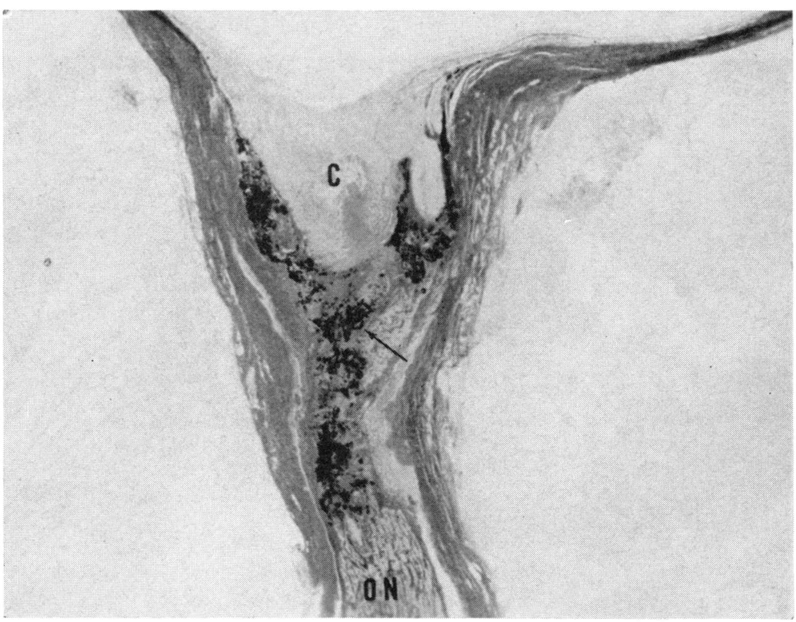

FIGURE 26

Pigmentation in coloboma of the optic nerve (ON). The pigmented epithelial lining of the coloboma (arrow) is the result of dysplasia of the cells of the normally non-pigmented outer layer of the primitive neural optic cup. The cupped optic disc (C) is filled with dysplastic sensory retinal elements. AFIP Neg. 64–6252 ($\times$ 9) extensive fibrous and osseous metaplasia was found within or at the edge of the defect (Figure 27). According to Coats[59] the inner and outer layers of the neural portion of the optic vesicle differentiate in such eyes to form structures normally found only in the globe. Thus, pigmented epithelium lines the pial sheath and malformed retinal elements are found deeper in the nerve, both layers being the result of dysplasia rather than hyperplasia. Ophthalmoscopic evidence of pigmentation, either at the edge of the nerve or within it, should be helpful in distinguishing these congenital defects from various other lesions characterized by atrophy and cupping.

Congenital dysplasias of the retina and optic nerve have also been mistaken for neoplasm. A cystic lesion was seen in the vitreous anterior to the papilla in one eye of a six-year-old child. It was surrounded by pigment and the eye was enucleated because a tumor of the optic nerve was suspected (Figure 28). The coloboma of the nerve was filled with malformed retina. Pigmentation was apparently caused by dysplasia of the pigment epithelium. A similar eye has been described by Seefelder.[60]

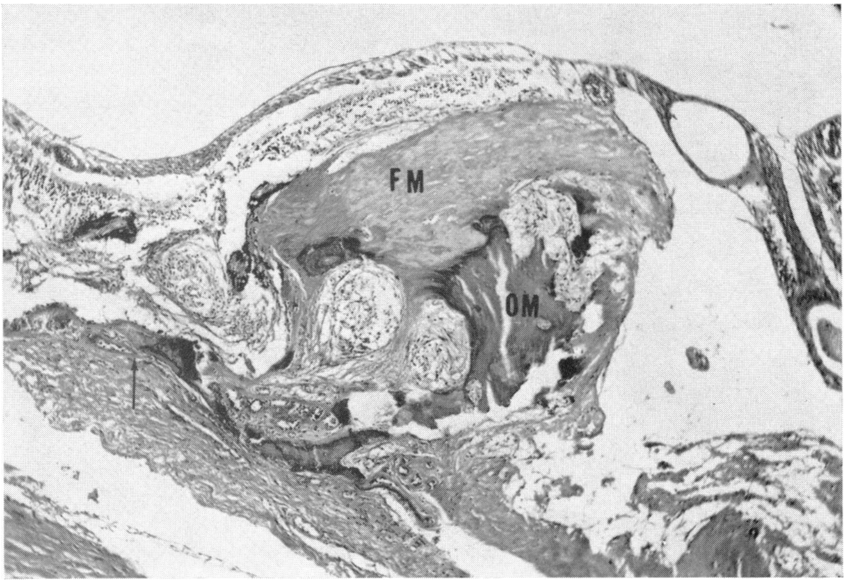

FIGURE 27

Coloboma of the optic nerve. At the margin of the coloboma are large mounds of fibrous (FM) and osseous metaplasia (OM). The arrow marks the termination of Bruch's membrane. AFIP Neg. 64–6266 ($\times$ 40)

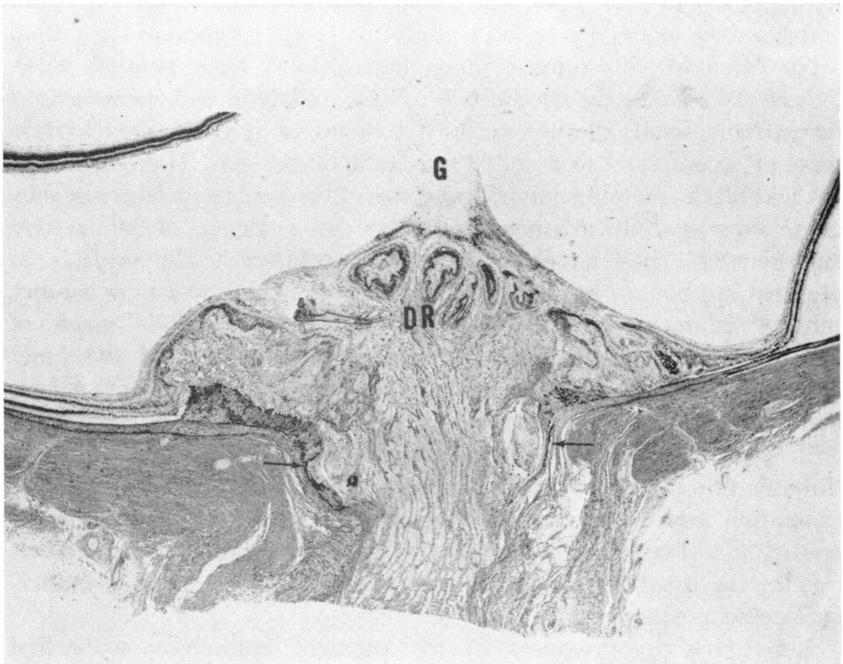

FIGURE 28

Multiple anomalies simulating a tumor over the optic disc of a six-year-old girl. The coloboma of the optic nerve (between arrows) is covered by a mass of dysplastic retina (DR). A glial stalk (G) extending into the vitreous clinically resembled a cyst. Pigmentation at the margins helped to convince the examiner that a tumor was present. AFIP Neg. 64–6242 ($\times$ 13)

Isolated patches of retinal pigmentation were found by Reese and Jones[61] in nine of one hundred and fifty-one eyes in which the diagnosis of malignant melanoma had been seriously entertained. These lesions, which they called benign melanomas of the pigment epithelium, were flat and sharply outlined and showed no evidence of any visual defect in the area involved. In the one eye which they examined histologically, the pigment epithelium was duplicated and heavily pigmented. There was also excessive pigmentation in the choroid beneath the lesion. Kurz and Zimmerman[10] described lesions which were similar except for the presence of a white halo surrounding the area of pigment. The small round plaques were characterized histologically by hypertrophy of the pigment epithelium and of the individual pigment granules but were without evidence of hyperplasia. No signs of inflammation were found in any of these eyes. The lesions were believed to be congenital and probably analogous to those of grouped pigmentation of the retina.

No examples of grouped pigmentation have been studied histologically. Clinically the condition is usually unilateral and characterized by variably sized, sharply outlined patches of grayish pigmentation most often confined to a single quadrant of the eye. The lesions are flat and often resemble animal footprints. Like benign melanomas they cause no visual disturbances and show no evidence of progressive enlargement. They have usually been attributed to hyperplasia of pigment epithelium in plaques filling defects in the overlying sensory retina.[27] Mann,[56] however, believed that they were the result of improper differentiation and subsequent pigmentation of the inner layer of the optic cup while Lindsay[62] held that they were a congenital version of the *tâches noirâtres* sometimes seen in association with uveal melanomas. Pigment epithelial cells, he believed, migrated through the subretinal space during a period of embryonic retinal separation and were deposited on the undersurface of the neuroepithelium where they proliferated to form pigmented plaques. Their quadrantic distribution corresponded to the falciform shape of embryonic detachments.

Hereditary pseudotumors of the pigment epithelium were first described as an entity by Norrie in 1927.[63] The condition has been given the name Norrie's disease[64] and is believed to be a result of a defect in the X-chromosome.[65] Members of the affected families have shown complete retinal detachment due to massive hyperplasia of the pigment epithelium of the retina.

3. *Inflammation and Hyperplasia*

Among the most dramatic and extensive hyperplastic changes of the pigment epithelium seen during this study were those produced by various forms of inflammation. Since lesions of this type were usually seen histologically in their late stages, at a time when specific etiologic diagnosis was rarely possible, analysis of the effects of inflammation on the pigment epithelium was of limited value in the solution of clinical problems.

The pathologic and clinical features of pigment epithelial hyperplasia, regardless of cause, depended in part upon the intensity of the stimulus. In focal chorioretinitis, for example, the concentration of the offending agent was apparently so great in the central portion of the lesion that it sometimes completely destroyed the retina, pigment epithelium, and choroid. In more peripheral portions of the same lesion, however, where the agent was diluted, it acted as a stimulus and massive proliferation of the pigment epithelium was frequently found. Such lesions were described clinically as white areas surrounded by a ring of hyperpigmentation.

Conversely, in some eyes inflammation was so mild that it provided only stimulation without destruction in any of its parts. The result was a gradually enlarging, uniformly pigmented lesion easily mistaken for melanoma. For example, in a fifty-four-year-old man complaining of gradual loss of central vision, a pigmented lesion about one-quarter the size of the optic disc was found just above the macula. Because the area of pigmentation continued to grow during the next three and a half months, the eye was enucleated with a tentative diagnosis of malignant melanoma. A proliferative lesion of pigment epithelium was found with a chronic inflammatory reaction in the choroid beneath it. Similar lesions were described by Fry and Spaeth[66] who compared their features with those of malignant melanoma. They found that pigmentation, caused by proliferation of the pigment epithelium, increased progressively in subacute macular retinochoroiditis but was not a prominent feature of malignant melanoma.

The duration of the inflammatory process was also found to be important in determining the characteristics of the accompanying hyperplasia. Chronic inflammation stimulated slow, continuous, and sometimes extensive hyperplasia while producing minimal clinical evidence of inflammation. When the pigmented lesion so produced was focal it could arouse the suspicion of melanoma and lead to enucleation (Figure 29). In eyes which had become phthisical as a result of prolonged inflammation, proliferation of the pigment epithelium reached astonishing proportions sometimes nearly filling the globe with sheets and tubular structures closely resembling those found in true neoplasms of the pigment epithelium.

Location of an inflammatory lesion also determined to some extent the characteristics of pigment epithelial reaction, a fact of some diagnostic importance. In this pathologic study the majority of inflammatory and degenerative lesions leading to enucleation because of suspected melanoma were found in the central part of the posterior pole. These diseases seemed to have produced a more intense effect on the tissues of the macular area than on any other. This regional difference has been attributed to the special characteristics of Bruch's membrane and of retinal and choroidal circulation in the macula.[67]

Although hyperplasia of the pigment epithelium was a frequent feature of chronic inflammation it was not specific and, in most eyes,

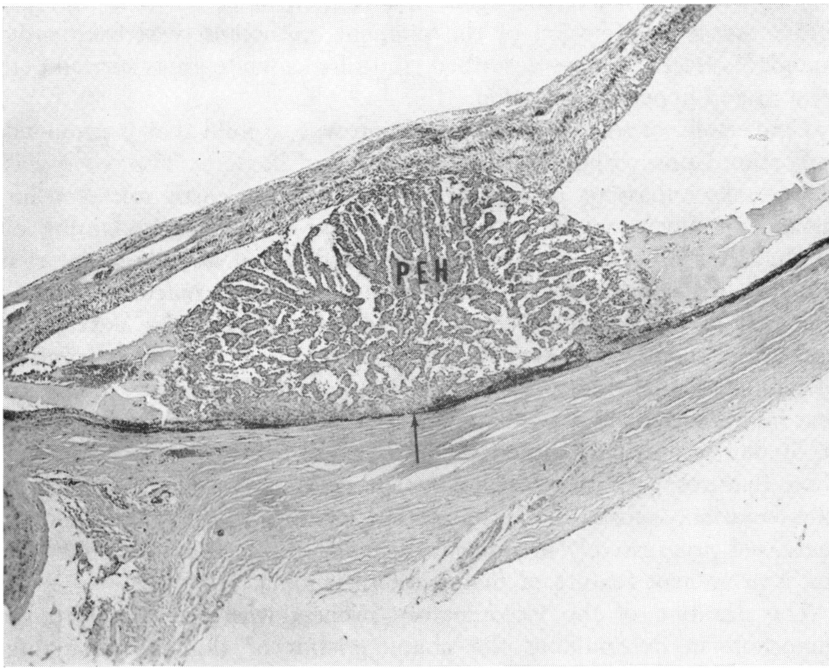

FIGURE 29

Pseudoepitheliomatous hyperplasia (PEH) in chronic chorioretinitis. There were minimal clinical signs of inflammation and the mass was mistaken for an expanding neoplasm. Cells are growing in cords separated by fibrous septa and their origin can be traced to the pigment epithelium. Bruch's membrane and choroid have been partially destroyed by the inflammatory process (arrow). AFIP Neg. 61–5456 (× 23)

could not be distinguished in its healed stage, even histologically, from that produced by degenerative or traumatic lesions. An exception to this rule was found, however, in one group of inflammatory diseases characterized by a rather specific clinical appearance. Rubeola, rubella, and vaccinia produce a granular pigmentation in the macular region and a peripheral pseudoretinitis pigmentosa.[68] Small groups of hyperplastic pigment epithelial cells have been found in these areas in eyes with rubella retinitis[69] and are believed to be responsible for the clinical features of the disease (Figure 30).

4. The Pigment Epithelium in Degenerative Disease

Clinical descriptions of retinal degeneration have universally emphasized alterations of pigmentation as one of the most prominent

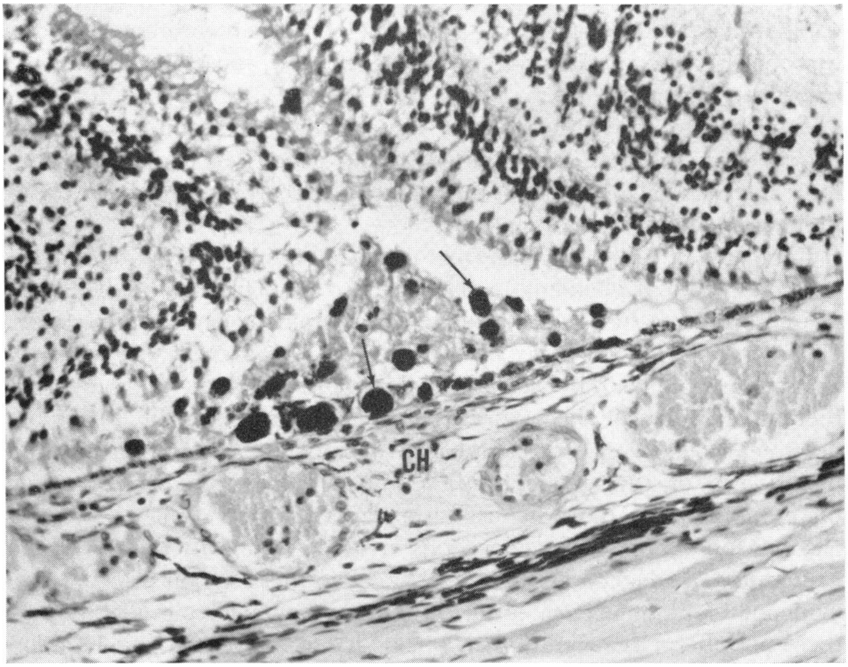

FIGURE 30

Granular pigmentation in congenital rubella retinitis. The section is from the macular area and shows small clumps of heavily pigmented cells beneath the retina (arrows). No significant scarring is evident. CH = choroid. (Section courtesy of Dr. Milton Boniuk, Baylor University.) (× 200)

features. Many similarities are noted between changes occurring in the macula and those found in the peripheral portions of the retina. The role of the pigment epithelium in the pathogenesis of retinal degenerations will be more easily understood, therefore, if both areas are considered together.

Klien[70] proposed the following classification for macular degeneration but its principles might also be applied to peripheral lesions.

a) True heredodegenerative diseases: (1) some primarily and selectively affecting the pericipient retinal elements; (2) some affecting the probably genetic unit of choriocapillaris, pigment epithelium, and neuroepithelium; (3) some representing the end stages of vitelliform degeneration.

b) Degeneration of the percipient retinal elements secondary to:

(1) diffuse and pronounced thickening and degeneration of the intercapillary connective tissue; (2) damage to Bruch's membrane; (3) disturbances in the vascular supply of the choroid, more specifically the choriocapillaris.

Attempts to study the role of the pigment epithelium in retinal degenerative diseases were limited by the paucity of available pathologic material. The study was supplemented, therefore, by a review of previously reported experience.

Early loss of vision characterizes primary heredodegeneration of the percipient retinal elements in the macular area. Pigmentation has no characteristic pattern and is usually not prominent in the early stages. Degeneration of the neuroepithelial cells, apparently the primary change, is followed by secondary hyperplasia of the pigment epithelium. In some of the eyes examined histopathologically, when the percipient elements had completely disappeared, degeneration and hyperplasia of the pigment epithelium produced connective tissue plaques similar to those in disciform degeneration.

In peripheral heredodegenerations involving primarily the rods, such as pigmentary degeneration, disturbances in night vision also precede evidence of pigmentation often by many years. The pigmentation in these peripheral degenerations is secondary to the retinal degeneration and assumes a characteristic pattern presumably determined by the arrangement of glial and vascular structures.[71] Migration of free pigment and pigment epithelial cells into the retina was described by Sorsby[72] as a scavenging mechanism and occurs, according to Reese,[9] whenever there is loss of continuity of the external limiting membrane.

Pigmentation of the retina was seen also in other heredodegenerations accompanied by degeneration of the neuroepithelium. In an eye from a child with the juvenile form of amaurotic familial idiocy (Batten-Mayou) the most prominent feature was a lipoidal degeneration of the ganglion cells but extensive pigmentation was present, both in the macula and in the peripheral retina, probably secondary to degeneration of the rod and cone layer. The histologic changes in the periphery were identical with those of primary pigmentary degeneration.

Heredodegeneration involving the choriocapillaris, pigment epithelium, and neuroepithelium as a genetic unit, was represented in Klien's study by the condition known as central areolar choroidal sclerosis. It was recognized clinically by the presence of sharply outlined, round or oval areas of pigment epithelial atrophy in the central retina, through which larger choroidal vessels could be seen as white cords. Patchy areas of hyperpigmentation were sometimes seen but were not of diagnostic importance. The only histologic reports available are those by Ashton,[73] Klien,[70] and Howard and Wolf[74] all of whom agree that central areolar choroidal atrophy would be a better term since the condition is distinguished by complete atrophy of the choriocapillaris, pigment epithelium, and neuroepithelium. In the eyes reported by Howard and Wolf, there was atrophy of Bruch's membrane. The large choroidal vessels are prominent because of pigment epithelial atrophy and appear white, Ashton believes, because of changes in the perivascular tissues rather than because of arteriosclerosis.

Other pigmented lesions of the macula have been attributed by various authors to primary hereditary degenerations of the pigment epithelium itself. Doyne's honeycomb degeneration has been the prototype for this category. In contrast to those forms of degeneration in which the neuroepithelium is primarily involved, visual disturbances in honeycomb degenerations occur long after the initial appearance of multiple colloid excrescences and pigment epithelial hyperplasia.[75] Pigmentation, according to most available descriptions, does not occur in a characteristic pattern and diagnosis depends upon the appearance of the colloid excrescences and upon establishment of a genetic background.

In the third group of heredodegenerations of the macula Klien included vitelline degeneration of the macula since its etiology was unknown. Only one histopathologic specimen has been described.[76] The eye was obtained in the late stages of the disease and degenerative changes in the retina and pigment epithelium were not specific. In a recent clinical review Braley and Spivey[77] described numerous variations in pigmentation with usually remarkable retention of visual acuity. They believed the disease was initiated by a degeneration of Bruch's membrane with eventual secondary degeneration of the pigment and neuroepithelial layers.

Macular degeneration occurring in the absence of a demonstrable hereditary background has been attributed to many factors including retinal circulatory stasis,[78] thickening of the lamina vitrea by hypersecretion of the pigment epithelium,[9] and occlusion of the choriocapillaris.[79] Friedman and Smith[80] noted, in normal senile eyes, zones of atrophy of the choriocapillaris and thickening of the intercapillary connective tissue beneath Bruch's membrane. Capillary atrophy was not, they believed, the result of occlusion of choroidal arterioles.

Klien[70] also found thickening of intercapillary connective tissue; she suggested that it might inhibit diffusion of nutrient substances through the membrane causing degeneration of pigment epithelium and of percipient elements of the retina. She saw these changes as an intensification of the physiologic aging process.

The early stages of the senile type of macular degeneration are marked by changes in pigmentation similar to those of the heredodegenerations but are often accompanied by minimal loss of vision. Histologically, the pigment epithelium in the few eyes available showed degeneration and hyperplasia and sometimes there was marked thickening of the cuticular portion of Bruch's membrane. Thick connective tissue plaques developed beneath the retina in the late stages of this disease as well.

The importance of degenerations of Bruch's membrane in the pathogenesis of various macular lesions was emphasized by Spencer[81] who found thickening, granularity, basophilia, and fragmentation of this layer in eyes of aging individuals. Concurrent changes were found in the overlying pigment epithelium. Fractures occurring in a calcified membrane have also been established as a precipitating cause of angioid streaks[82,83] and of disciform degeneration of the macula.[28] The cause of the dark but variably colored appearance of angioid streaks has not been clearly established. In some of the eyes examined during the course of this study the broken areas of Bruch's membrane were covered by extensive areas of hyperplasia and metaplasia of the pigment epithelium (Figure 31); in others, only the break in the lamina vitrea was visible with virtually no reactive changes in adjacent tissues (Figure 32). The clinical appearance in these two extremes might be expected to differ significantly. Verhoeff believed that the dark color was due to the contrast between the brightened reflex from the calcified lamina vitrea and the darker area of dehiscence. Cowper[84] denied the ruptured membrane theory suggesting instead that angioid streaks were really choroidal veins. After injection of fluorescein, however, angioid streak areas fill during the arterial phase, an indication that they cannot represent venous structures.[85]

Breaks in Bruch's membrane, particularly when in the macular area, might lead also to sudden development of a hematoma beneath the pigment epithelium,[86] a lesion which has been said to resemble uveal malignant melanoma more closely than any other. The dark gray or green color of the mass in such eyes is imparted by the pigment epithelium and by the blood beneath it. The true nature of the lesion usually becomes evident only when blood breaks through the pigment

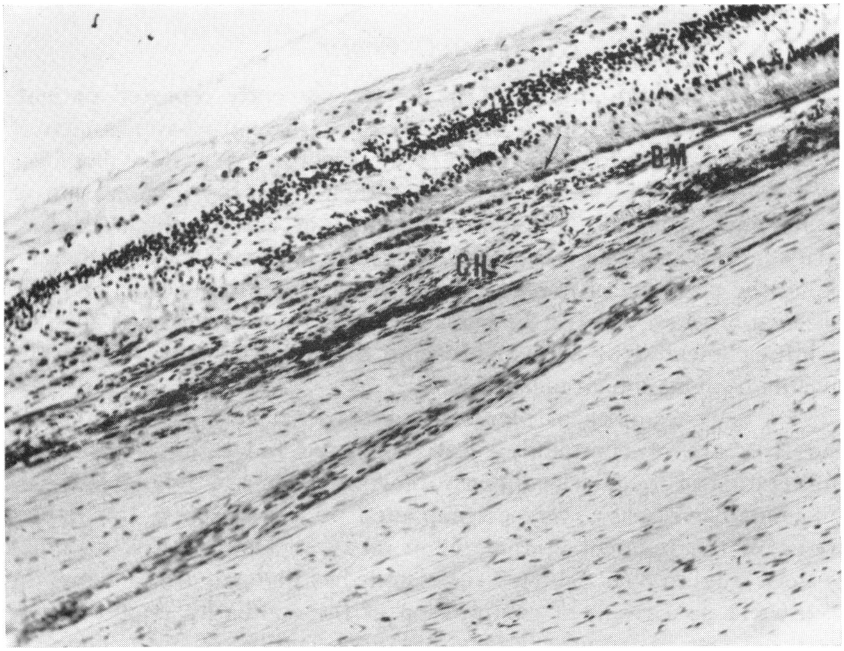

FIGURE 31

Angioid streaks. Bruch's membrane (BM) shows marked basophilia and is absent in a large portion of the field. Granulation tissue has extended from the choroid (CH) into the subretinal space displacing pigment epithelium ahead of it. AFIP Neg. 64–6250 (× 115)

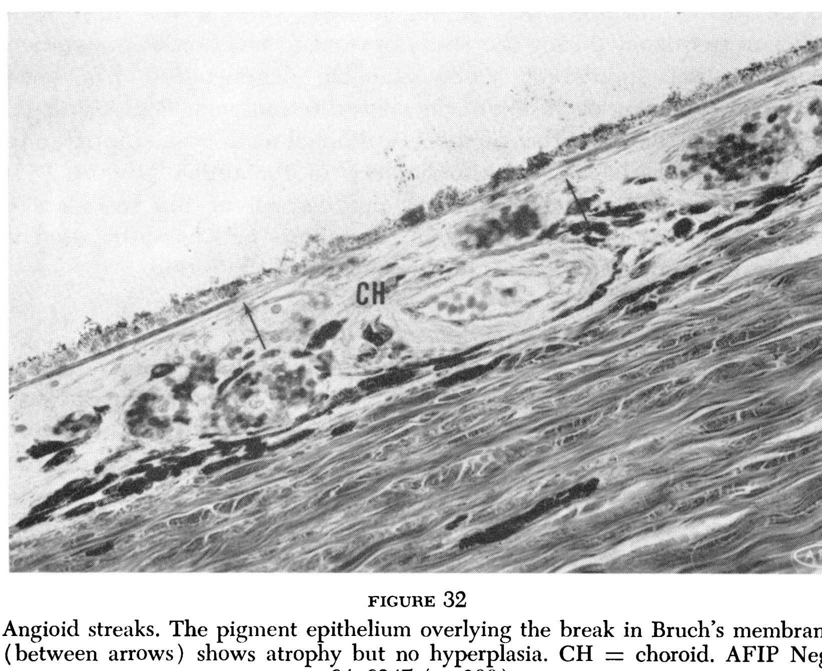

FIGURE 32

Angioid streaks. The pigment epithelium overlying the break in Bruch's membrane (between arrows) shows atrophy but no hyperplasia. CH = choroid. AFIP Neg. 64–6247 (× 300) epithelium into the subretinal space. One recently reported patient, however, developed a dark mass only after the initial appearance of hemorrhage.[87] Gradual expansion of the lesion led to a false diagnosis of melanoma. The role of pigment epithelium in the organization of hematomas beneath the pigment epithelium and in the subretinal space has already been discussed. Absence of extensive serous detachment, the presence of hemorrhage adjacent to the lesion and, usually, absence of pigment over the surface of the lesion have been cited as helpful clinical signs in distinguishing disciform degeneration of the macula from malignant melanoma.[88]

Very few examples of pigmented lesions caused by alterations in the structure of choroidal vessels could be found. Focal areas of obliteration of the choriocapillaris, however, either by degenerative or inflammatory disease, were accompanied by degeneration and hyperplasia of the pigment epithelium in areas adjacent to the occluded vessels (Figure 33). Ashton[73] suggested that pigmented lesions might also occur as a result of compression of the capillaries possibly by a localized extravasation in the choroid. Such lesions did not necessarily imply sclerosis or occlusion of a posterior ciliary artery. Histologically recognizable forms of arteriosclerosis of the larger arteries of the choroid, even those causing complete obliteration, were not accompanied by significant changes in the pigment epithelium.

One further manifestation of degenerative disease was seen with sufficient frequency during this study to warrant mention. Pigmentation in the retina simulating senile macular degeneration has been described following occlusion of the central retinal vein.[89] In histologic specimens changes in the pigment epithelial cells were apparently secondary to marked atrophy and gliosis of the retina (Figure 34). Wise has emphasized the apparent predilection of the macula for many of the residua of central vein thrombosis and has attributed it to the greater metabolic needs of this portion of the retina.

5. *The Retinal Pigment Epithelium after Trauma*

No changes in the pigment epithelium have been known which are entirely specific for trauma. Although study of the histopathology of eyes which had been subjected to traumatic injury revealed many extensive and varied manifestations of pigment epithelial hyperplasia, the changes were similar in most respects to those accompanying inflammatory or degenerative disease. A disseminated form of pigmentation superficially resembling retinitis pigmentosa was seen in severe contusion injuries of the globe and was apparently caused by

FIGURE 33
Degeneration and hyperplasia of retinal pigment epithelium (PE) caused by necrotizing arteriolar sclerosis of choroidal arterioles (arrows) in a patient with severe hypertension. HUP Acc. No. 1013 ($\times$ 125)

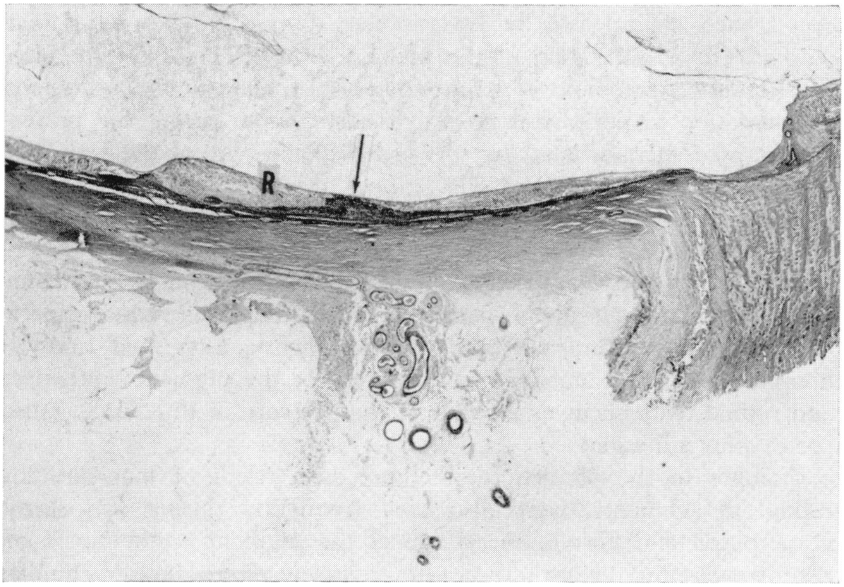

FIGURE 34
Hyperplasia of pigment epithelium (arrow) in the macular area following occlusion of the central retinal vein. The overlying retina (R) is atrophic. Clinically the lesion resembles a macular degeneration. AFIP Neg. 64–6249 ($\times$ 11)

the pigment epithelium reacting to necrosis in adjacent tissues. Less severe contusion produced only a granular pigmentation of the macula presumably also a result of damage to the pigment epithelium.[90]

Occasional examples of complete holes in the macula, resulting from contusion injuries, were found during the pathologic study. Such macular damage stimulated surprisingly little reaction by the pigment epithelium. In spite of this, very few retinal detachments resulting from macular holes have been reported[91] possibly because the vitreous exerts limited traction on the retina in this area.[92]

After choroidal rupture, hyperplasia of the pigment epithelium was usually limited to a small area necessary to produce an effective chorio-retinal adhesion and clinical diagnosis depended on the crescentic shape of the lesion. Hagedoorn[93] reported an eye with a traumatic rupture of pigment epithelium alone. Bruch's membrane in this eye was intact. The lesion was described ophthalmoscopically as a thin, yellowish crescentic line with little or no accompanying pigmentation.

6. The Pigment Epithelium in Retinal Detachment

Recent attention has been directed to the importance of peripheral retinal degeneration in the pathogenesis of retinal separation. Clinical and pathologic studies have described degenerative areas of variable appearance caused usually by vascular disease in the retina and choroid.[94-96] Proliferation of the pigment epithelium in degenerative areas often contributed to the formation of firm chorioretinal adhesions. Pigmentation in peripheral areas was also found during the present study apparently initiated by forward displacement of the retina by vitreous contraction (Figure 35).

Vitreous traction at the site of chorioretinal adhesions has been most often cited as the cause of tears in adjacent normal retina.[97] A significant body of opinion has held, however, that the pigment epithelium plays a primary role in the pathogenesis of idiopathic retinal separation.[11,98,99] The retina, according to this theory, is pushed from its normal position by an abnormal secretion of the pigment epithelium and retinal tears occur as a result of the pressure of this fluid against pre-existing adhesions.

Changes in the pigment epithelium, as a result of long-standing retinal detachments, were also seen frequently during this study. Hyperplasia and fibrous metaplasia of the pigment epithelium completely encircling the ora serrata (*Ringschwiele*) were common. Similar structures were found in some eyes surrounding the optic disc and had occasionally been mistaken for tumors. The question of melanoma

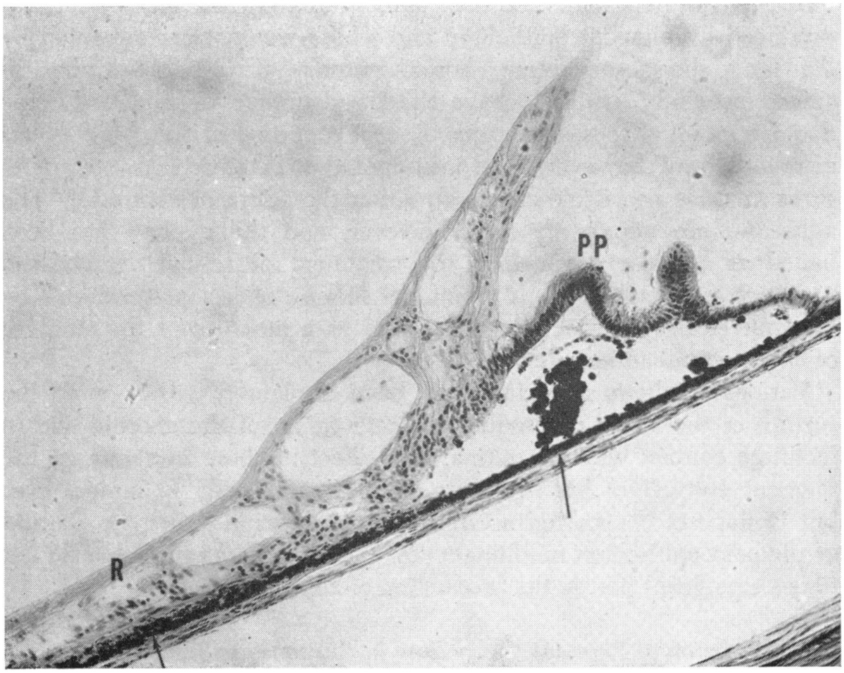

FIGURE 35
Peripheral degeneration accompanied by proliferation of retinal pigment epithelium (arrows). Lesions are apparently induced by vitreous contraction. The pars plana (PP) is also detached. R = retina. HUP Acc. No. 1289 ($\times$ 100)

arose in one eye of a patient with a large serous retinal detachment because two dark masses could be seen behind the retina immediately adjacent to the optic nerve. The retinal separation prevented a good view of them and transillumination was not practical. After the eye was enucleated the pigmented tumors proved to be small nodules of pigment epithelium and connective tissue beneath the retina.

Migration of the pigment epithelium through retinal tears and onto the anterior surface of the retina and its participation in the formation of preretinal membranes have already been discussed. Contraction of these membranes produced fixed folds in the retina which might have altered materially the course of treatment by preventing the retina from returning to its normal position against the choroid.[100]

Successful surgical repair of retinal detachments requires effective closure or isolation of retinal tears. This objective has been accomplished so far only by methods which create adhesions between the retina and the choroid. The ideal adhesion would be one which was produced by pigment epithelium and which was not accompanied by damage to the sensory retina, choroid, vitreous, or sclera. Most physical agents presently available have the disadvantage of inflicting some damage on all of these structures. Recent reports describing the effects of cryotherapy, however, have indicated that extremely low temperatures produce no visible effects on either the sclera or choroid.[101] The adhesions are apparently firm, however, and the method has been hailed as a major advance in the treatment of retinal detachment. Although pigmentation is a prominent feature of lesions produced by such physical agents, it cannot be used as a measure of the strength of chorioretinal adhesions.

Various synthetic materials have been implanted within or on the surface of the sclera to produce an indentation of the choroid and to facilitate contact with the retina. The effect of these implants on the pigment epithelium has not been studied specifically in human eyes but Dellaporta[102] reported no significant changes in either the choroid or pigment epithelium in animal eyes. These implants probably do not play a significant part in the production of adhesions.

7. *Proliferation of Pigment Epithelium in Response to Tumors*

Pigmentation was a prominent clinical sign in many eyes removed because of a mistaken diagnosis of malignant melanoma and, in most instances, proved to be the result of pigment epithelial proliferation. Reese[103] has stated that the jet black color of pigment epithelial pigmentation should not be confused with the brownish pigment of true uveal melanomas. In the present study, however, large areas of pigment epithelial hyperplasia were found frequently overlying benign and malignant neoplasms of the choroid and might well have obscured these differences in color. Such pigmentation over the surface of choroidal tumors was usually the result of degeneration, hyperplasia, and metaplasia of the pigment epithelium. These changes were invariably found whenever the tumor invaded the choriocapillaris and were clearly not an indication of malignant change. Thus, a number of choroidal nevi with benign cytologic characteristics were accompanied by extensive alterations in the pigment epithelium but only when the nevus had reached the layer of choroidal capillaries.

Occasionally, both nevi and malignant melanomas were accompanied by large connective tissue plaques reminiscent of those found in disciform degeneration of the macula. In one eye the disciform lesion was found overlying a benign nevus (Figure 36). In two other

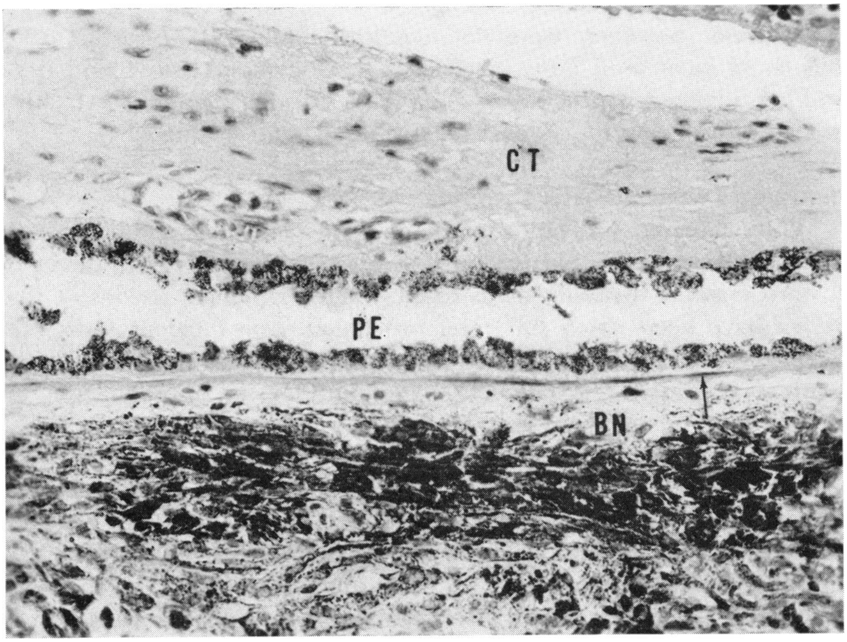

FIGURE 36

Lesion resembling disciform degeneration overlying a benign nevus (BN) in the choroid. Pigment epithelium (PE) is present in a double layer with newly formed connective tissue (CT) in front of it. The choriocapillaris is partially invaded by the nevus and Bruch's membrane shows small areas of calcification (arrows). AFIP Neg. 62–5154 (× 305)

eyes, one with a nevus and the other with a malignant melanoma, the degenerative changes were found at some distance from the tumor. It is of interest that in both patients the eye was enucleated because the connective tissue tumor was thought to be a melanoma and, in both, the true neoplasm had been overlooked.

In addition to degenerative areas overlying the tumor, Kurz and Zimmerman[10] found diffuse hyperplasia of pigment epithelium in the area of a secondary retinal detachment. Discrete plaques of hyperplastic pigment epithelium, also in areas of secondary retinal detachment, had been described first by Zeeman[104] who called them *tâches noirâtres.* He believed them to be the result of subretinal migration of pigment epithelial cells from the area of the tumor. They have been cited as a valuable diagnostic sign.[105]

Pigmentation within the retina and on its anterior surface was also seen accompanying some melanomas. Cells containing pigment in these areas, however, were not necessarily pigment epithelial cells but could have been large macrophages. One report was found describing pigment epithelium which had allegedly migrated to the vitreous producing the clinical picture of asteroid hyalitis.[106]

8. *Retinal Pigmentation in Drug Intoxications*

With increased utilization of many new chemotherapeutic agents in the treatment of various systemic diseases, interest has been directed toward possible toxic effects of these drugs. Pigmented lesions of the retina have been noted following prolonged use of chloroquine, NP 207, and Thioridazine. Although few histologic descriptions have been made, it is evident that pigment epithelium plays an important role in the pathogenesis of these changes.

The characteristic lesion of chloroquine retinopathy was first described in 1959[107] as a focal area of depigmentation of the macula surrounded usually by a ring of pigment. Retinal arterioles showed marked attenuation and fine deposits of pigment were found in the periphery. Histologic reports[108–110] described atrophy of the rod and cone layer and of the pigment epithelium. Pigmented cells were found in the outer layers of the retina.

Bernstein and his associates[111] demonstrated a high concentration of chloroquine in the uveal tissues and in the pigment epithelium of animals. They suggested that the drug was bound to the pigment granules in these cells thus inhibiting the metabolism of the pigment epithelium and resulting in secondary degeneration of rods and cones. Yanoff and Tsou,[112] reporting the results of enzyme studies in tissues incubated with chloroquine, concluded that the drug acted by interference with the cytochrome oxidase system. The retina might be selectively damaged because of its high oxygen requirements.

Other drugs have also demonstrated preferential binding by the melanin pigment and all could theoretically produce a retinopathy.[113] McFarland, Yanoff, and Scheie[114] recently described an example of toxicity in a patient treated with Sparsomycin, an experimental anticancer chemotherapeutic agent. The retina and pigment epithelium showed histologic and clinical changes similar to those produced by chloroquine (Figure 37).

9. *Radiant Energy and the Pigment Epithelium*

No significant contribution concerning changes produced by radiant energy on the pigment epithelium could be included in this report

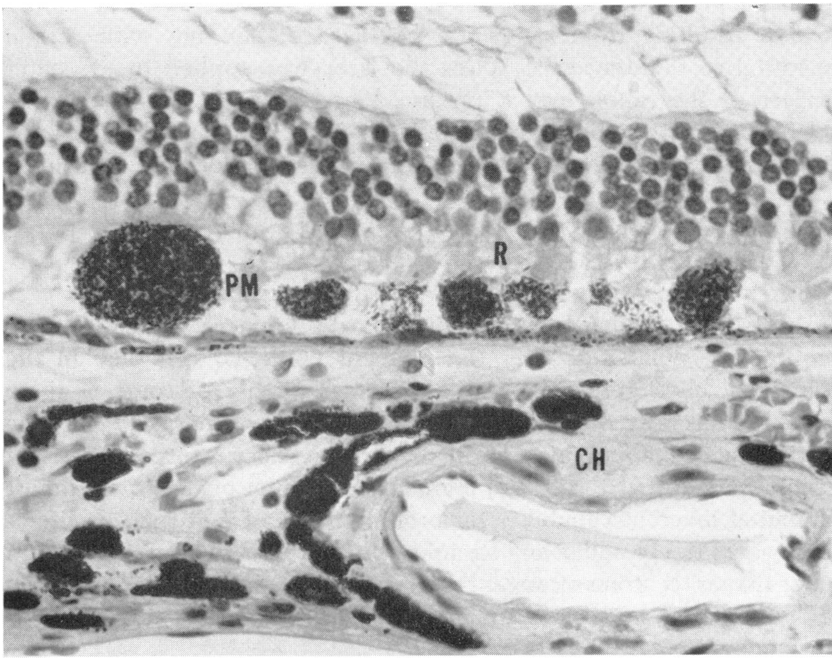

FIGURE 37
Toxicity to Sparsomycin in a human eye. There is marked atrophy of the pigment epithelium and percipient elements of retina (R). Large pigment-laden macrophages (PM) are found in the subretinal space in the perimacular area. The distribution of pigmentation is similar to that in chloroquine retinopathy. CH = choroid. AFIP Neg. 64–6613 (× 485)

because of the paucity of human pathologic material. A brief review of the comparative effects of photocoagulation and laser burns in the experimental animal seemed pertinent, however, in view of the recent interest in clinical uses of these techniques.

The principal disadvantage of most methods used to produce chorioretinal adhesions or to obliterate pathologic lesions of the fundus has been the extensive damage done to adjacent structures. Photocoagulation by the xenon arc lamp represented a step forward since it produced a burn primarily in the area of the pigment epithelium accompanied by relatively minor damage to the retina, choroid, and vitreous.[115] It could not be used, however, in the presence of significant vitreous opacities or retinal detachment. More recently, optical masers (lasers) have been introduced to produce controlled lesions of photocoagulation. In experiments using rabbits this very intense monochromatic light has produced a chorioretinal scar similar to that resulting from xenon arc photocoagulation but with certain quantitative differences.[116] When the laser was applied to the outer surface of the rabbit eye, it produced no significant damage to the sclera but did produce a chorioretinal scar.[117] Similar selective scars have now been achieved by the external application of extreme cold.[101]

SUMMARY AND CONCLUSIONS

1. THE GENERAL NATURE OF PIGMENT EPITHELIAL REACTIVITY

When, and under what conditions, do pigment epithelial cells proliferate? What part does the pigment epithelial cell play in the healing of chorioretinal wounds? A clearer picture of some of these processes has been obtained in my study by comparing histopathologic sections with the findings from tissue culture experiments. It has been generally held that the retinal pigment epithelium possesses an almost unlimited inherent capability for proliferation and that such proliferation occurs freely under any stimulus without material assistance from other tissues. It seems strange, therefore, that, in spite of the frequency of hyperplasia, neoplasms arising from the pigment epithelium are extremely rare.

The most important result of these tissue culture experiments was the discovery that the best outgrowth of pigment epithelial cells occurred when they were implanted on a monolayer of fibroblasts. In repeated experiments, a consistent outgrowth of pigment epithelial cells in the presence of fibroblasts contrasted significantly with the almost universal failure of outgrowth when these cells were cultured in the absence of such a supportive layer.

Although no valid comparison can be made between the behavior of cells *in vitro* and those in the living eye, I also noted repeatedly a similar pattern of cell growth in histopathologic specimens. In human eyes, pigment epithelial hyperplasia, except in primary neoplasms, was most extensive in the presence of some form of connective tissue. It was apparent that proliferation of pigment epithelium was stimulated or supported by other tissues, for example, vitreous collagen, preretinal membranes, or granulation tissue. I found minimal proliferation of the pigment epithelium in those degenerative lesions of the retina which were characterized by atrophy and accompanied by limited scarring. On the other hand, destructive lesions involving the choroid and Bruch's membrane were often accompanied by extensive scar tissue derived from vascular sources and were complicated by marked hyperplasia and metaplasia of the pigment epithelium.

The nature of the stimulus to pigment epithelial proliferation provided by connective tissue could not be determined from either the tissue culture experiments or the histopathologic sections. Further experimentation will be necessary to determine if the assistance was purely mechanical support or if it might have been some biochemical relationship between the two types of cells. It is clear, however, that the pigment epithelium is dependent on factors other than its own inherent ability to proliferate and that its reactivity is governed, to a large extent, by its surroundings.

The question of what role is played by the pigment epithelium in wound healing was also examined. It has been clearly established that pigment epithelium is active as a primary force in the healing of chorioretinal injuries. Results of my histopathologic study confirm the impression that, in this respect, these cells are analogous to fibroblasts in the body as a whole and to astrocytes in the central nervous system. It is believed that pigment epithelial cells produce collagen precursors and mucopolysaccharides which are important ingredients in the formation and organization of scar tissue. They also undergo metaplasia to form fibrous and osseous tissues. Although it is pure speculation, it is possible that pigment epithelial cells might also exert some control in the development of scars produced by fibroblasts from other sources.

2. ANALYSIS AND CLASSIFICATION OF OCULAR LESIONS IN WHICH PROLIFERATION OF PIGMENT EPITHELIUM PLAYS A PROMINENT PART

This study was concerned with all pigmented lesions of pigment epithelial origin. Particular attention was directed, however, to lesions which had been misdiagnosed as malignant melanomas and in which pigmentation, caused by pigment epithelial hyperplasia, contributed to the error in diagnosis. It has been repeatedly emphasized by others that pigmentation alone, or progressive enlargement of an elevated mass alone, are not sufficient evidence of malignancy to justify enucleation. Analysis of these lesions in my series amply confirmed this opinion. I was able to show that pigmentation, even when it was clinically described as progressive, can often be explained by proliferative changes in the pigment epithelium. Chronic inflammation, repeated hemorrhage, and the formation of new membranes frequently appeared to provide the necessary stimulus to pigment epithelial proliferation and, thus, to clinical evidence of progressive increase in the size of pigmented areas. Repeated careful examination of such eyes over a reasonable period of time should always be done before advising enucleation.

Although study of lesions commonly mistaken for malignant melanomas was the most important part of the analysis of ocular lesions characterized by pigment epithelial hyperplasia, other significant observations were made. Even true neoplasms of the choroid, benign as well as malignant, were frequently found to be accompanied by proliferation of pigment epithelium. These changes were apparently caused entirely by damage to surrounding tissues as a result of tumor growth and were clearly not a reflection of the nature of the tumor. Clinical evidence of patchy pigmentation overlying a nevus of the choroid, for example, should not be considered as an indication of malignant transformation.

The nature of the pigment epithelial response in all diseases was often found to be governed by the region of the choroid or retina involved as well as by the intensity and duration of the stimulus. The extent and histopathologic appearance, therefore, of lesions in which pigment epithelial proliferation participated was to a certain degree predictable.

3. THE CLINICAL VALUE OF PATTERNS PRODUCED BY PROLIFERATION OF THE RETINAL PIGMENT EPITHELIUM

It has been generally conceded that, in some diseases, pigmentation of the ocular fundus assumes patterns which may be sufficiently distinctive to be of real assistance in clinical diagnosis. For example, in primary pigmentary degeneration of the retina, the characteristic bone-corpuscle–like arrangement of pigment in the mid-periphery of the fundus is one of the most helpful clinical signs. Similarly, a ring of granular pigmentation surrounding the macula has now been recognized as a characteristic change in chloroquine toxicity. In most diseases, however, in which pigmentation is prominent, no specific or consistent pattern of pigment distribution can be found.

My own study confirmed the opinion of others that histopathologic changes in the pigment epithelium are also not usually specific for any single disease entity. Ophthalmoscopically visible pigmentation produced by these changes cannot reasonably be expected, therefore, to be of diagnostic value in most eyes. The general character of the pigment epithelial response was found to be predictable, however, in two broad categories of disease. Recognition of the differences existing between them might be of some clinical value.

One of these groups, including viral infections and heredodegenerative diseases, affected primarily the outer layer of the retina or the pigment epithelium. Lesions resulting from these diseases were characterized by destruction of the pigment epithelium but were usually free of extensive hyperplasia and metaplasia. Pigment from epithelial cells was usually found in small clumps of cells which might appear clinically as small granules.

In the other group were included various degenerative and inflammatory diseases characterized by their destructive effects on the choroid and Bruch's membrane. These diseases were found to be accompanied more often by extensive hyperplasia and metaplasia of the pigment epithelium as well as by scar tissue arising in the choroid. A large, elevated, pigmented lesion might, therefore, be seen clinically and would lead the examiner to suspect disease primarily in the choroid.

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